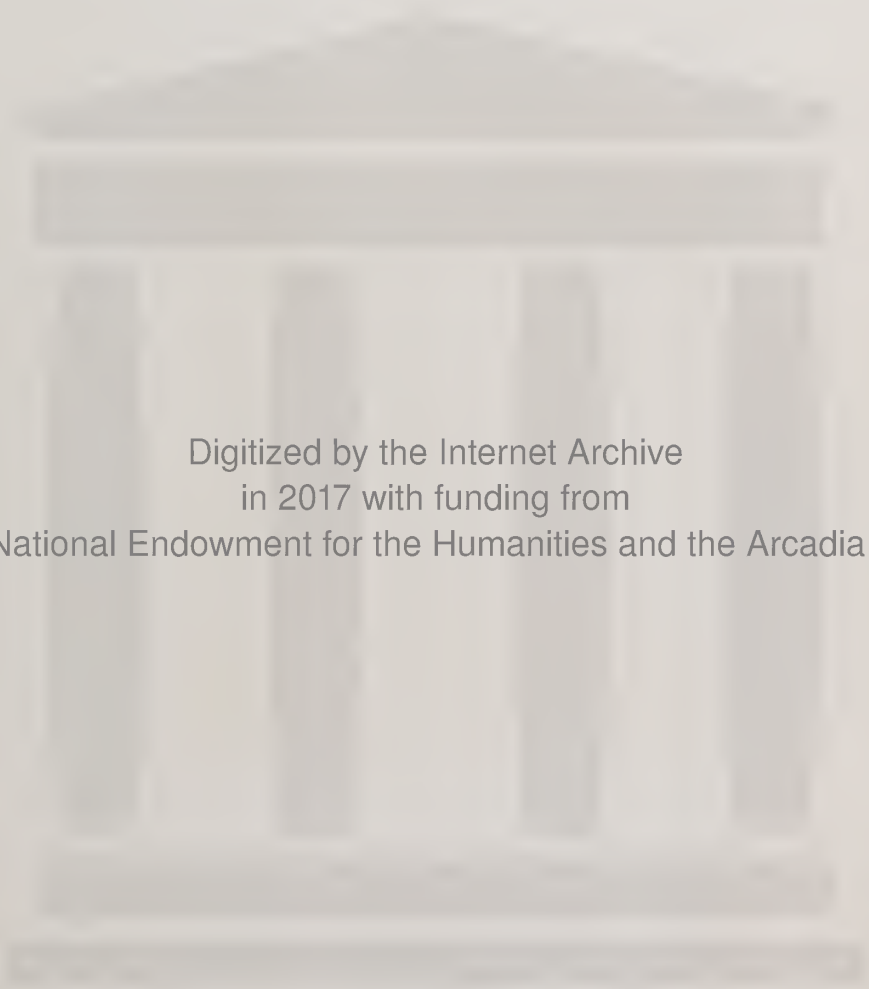
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BOLETIN

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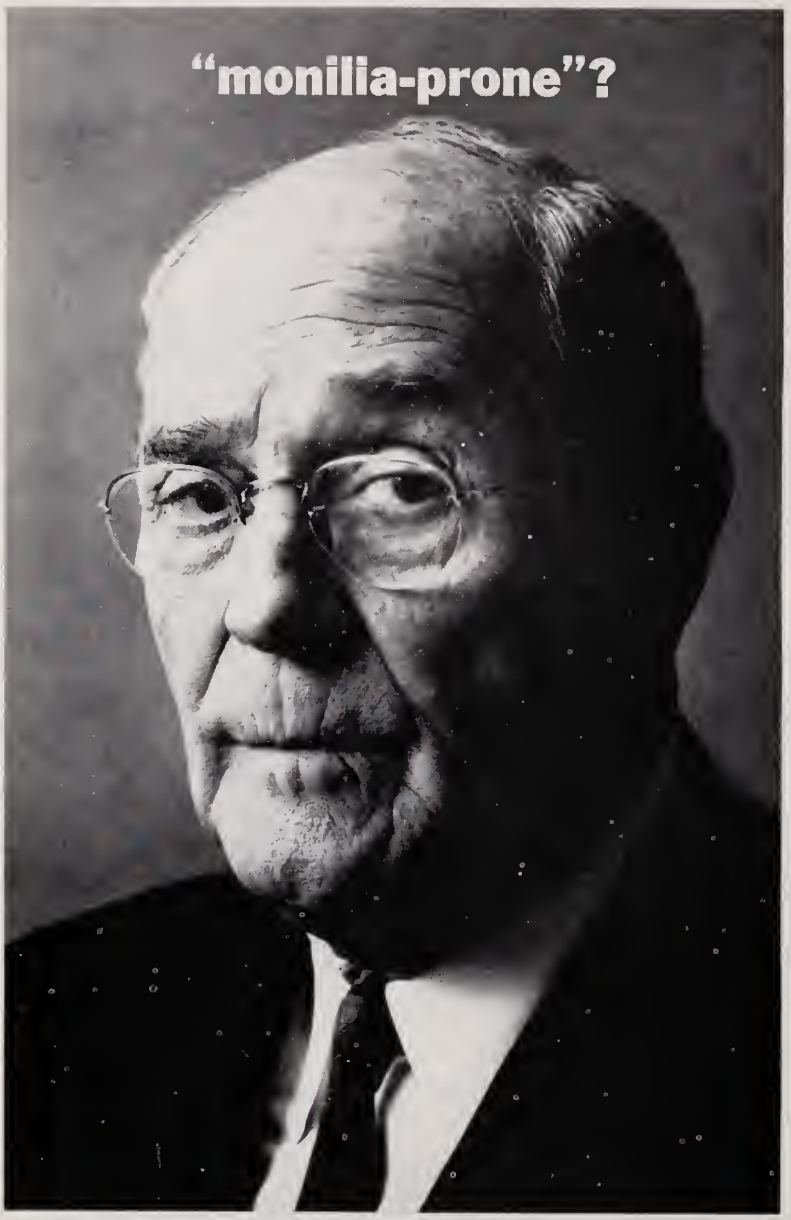
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EPILEPTIC HEADACHES

Luis P. Sánchez Longo, MD
Luis E. González Saldaña, MD

In 1941 Putman and Merritt (1) wrote a paper about mental lapses, recurring bouts of mental dullness or mild confusion occurring in episodic manner which they referred to as "epileptic equivalents". The electroencephalographic evidence brought forth in favor of an epileptic dysrhythmia was the presence of very slow brain-wave rhythms. These episodes are not to be confused with transitory mental lapses or confusion as seen in aborted grand mal and psychomotor seizures and during petit mal status.

The term "epileptic equivalents" is being mistakenly used to include other episodic phenomena including recurrent abdomenalgia (autonomic seizures), headaches (epileptic cephalea), enuresis, hyperactive behavior and many other behavior disturbances including neurotic and psychotic manifestations.

The term "masked epilepsy" has also been employed in patients suffering with one of the paroxysmal disorders included above under "epileptic equivalents".

Of this group we have been particularly interested in the problem of the episodic headaches and after seeing several cases in our clinic we felt it worthwhile reporting them as instances of epileptic headaches in an effort to further clarify the concept.

From the Section of Neurology, Department of Medicine and the Department of Pathology, University of Puerto Rico School of Medicine, San Juan, P.R.

Case Reports

Case 1: This patient is a 38 year old married female, who complained of recurrent, severe, episodic headaches since age 20.

The headache is localized in the left hemicranium particularly over the mastoid and occipital areas and described as constant, penetrating and non-pulsating. She claimed that occasionally the headache was precipitated by strenous physical activity and at times was relieved by taking analgesics with a sedative (Fiorinal). When we first saw her on september 14, 1963 the headaches were recurring once a week. There was no history of seizures, syncope, transitory confusion or mental dullness.

The past medical history was only significant in that she had an unexplained episode of unconsciousness during childhood and a history of peptic ulcer in the past. There was no family history of epilepsy, psychiatric disorders or episodic headaches.

The physical examination revealed a well-developed, well-nourished female, normotensive, in no acute distress. The pertinent findings were slight tenderness on palpation of the left mastoid and occipital areas, slight relative hypoalgesia of the left side of the face and slight ataxia when walking heel to toes in a straight line. The Weber hearing test lateralized to the right.

A preliminary diagnosis of a left-sided acoustic neurinoma was made. Audiometry revealed a slight

nerve-type of hearing deficit on the left. There was a 20-decibel loss of air and bone conduction to 250 and 500 cycles per second.

The caloric tests were negative. The skull series including special views for the mastoids and Stenvers were normal. The lumbar puncture was negative.

The electroencephalogram was abnormal (Fig. 1)

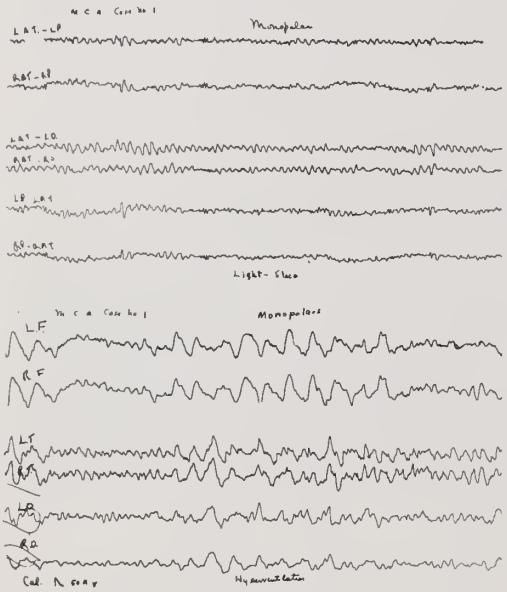


Fig. 1 (Case 1): EEG showing biphasic spikes and sharp wave discharges recorded in synchrony over both hemispheres particularly over both temporals, Rhythmic, high amplitude, slow delta activity with hyperventilation was also found.

Biphasic spikes and sharp wave discharges recorded in synchrony over both hemispheres particularly over both temporals and rhythmic, high amplitude, slow delta activity with hyperventilation, were found.

The diagnosis of acoustic neurinoma was ruled out because of the normal caloric test, normal skull series and spinal fluid.

The patient was placed on diphenyl hydantoin, 100 mgm. three times a day, and there was an immediate and prolonged improvement of her headaches. For the first time in years her headaches disappeared for over a year, but the medication was discontinued due to a reduction in platelet count. After cessation of treatment there was a return of recurrent headaches. This case was diagnosed as suffering sclerosis of the internal ear and mastoid on the left and epileptic headaches.

Case 2: The patient is a 16 year-old white male who gave a history of 2 episodes of photopsia followed by severe headaches and transitory loss of consciousness without convulsions. These episodes occurred 5 and 2 months prior to the neurological consultation. Following the original episodes, he continued suffering with frequent episodic headaches characterized by pain localized in the left eye and hemicranium, constant and pulsating, and frequently associated with blurring of vision. The past medical history was non-contributory. The family history revealed episodic headaches and blackout spells without convulsion in his grandmother and in one aunt.

The neurological examination was negative.

Routine laboratory work-up, skull series, blood chemistry and visual fields were normal. An electroencephalogram performed prior to the therapy was considered abnormal due to the presence of frequent paroxysmal discharges of synchronized parietal and temporal sharp waves.

The patient was placed on diphenyl hydantoin 100 mgm. t.i.d. and he has been free of episodes of unconsciousness and of severe headaches except during Christmas time 1964 when he discontinued the medication and had a recurrence of daily severe headaches, blurring of vision and dizziness.

At the time of this writing the patient develops occasional episodes of headache about every 2 weeks and the last EEG was interpreted as normal.

Case 3: This patient is a 10 year-old boy who has a history of generalized dull, but persistent headaches recurring with a frequency of one or two episodes per week for the past 3 years. These are relieved by sleep and at times by the use of analgesics. Occasionally the headache was associated with a subjective feeling of light-headedness. There was no history of unconciousness, convulsions, transitory episodes of mental dullness, confusion or behavior changes.

The past medical history revealed that this

patient apparently had encephalitis at 5 years of age while living in Perú. At that time he developed fever, lethargy, nuchal resistance, abnormal centrospinal fluid findings. An electroencephalogram following the febrile illness showed asymmetry between the hemispheres.

The family history is significant in that one of his brothers suffers with recurrent grand mal epileptic seizures and a grandfather is said to have epilepsy.

The physical and neurological examination were negative.

The routine laboratory studies and skull series were normal.

An electroencephalogram revealed abnormal high amplitude spikes and sharp wave discharges over the right occipital area. (Fig. 2).

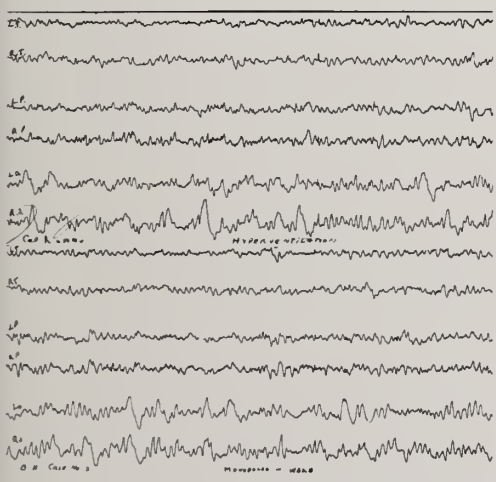


Fig. 2 (Case 3): EEG revealing abnormal high amplitude spikes and sharp wave discharges over the right occipital area.

The patient was placed on 30 mgm. of diphenyl hydantoin twice daily with complete remission of the headaches. Unfortunately we have not seen this patient again for the past six months.

Case 4: This patient is a 35 year-old married female who gave a history of recurrent occipital or left hemicranial headaches recurring in episodes every month or so for the past 2 years. At times her headaches, which are non-pulsating, are referred to the nuchal area.

The rest of her present and past medical history was negative. The family history revealed the occurrence of similar headaches in an aunt and in 2 cousins.

The physical and neurological examinations were negative.

The routine laboratory studies including blood chemistry were normal. A skull series and cervical spine x-rays were normal but an electroencephalogram showed high amplitude, right temporal spike discharges (Fig. 3).

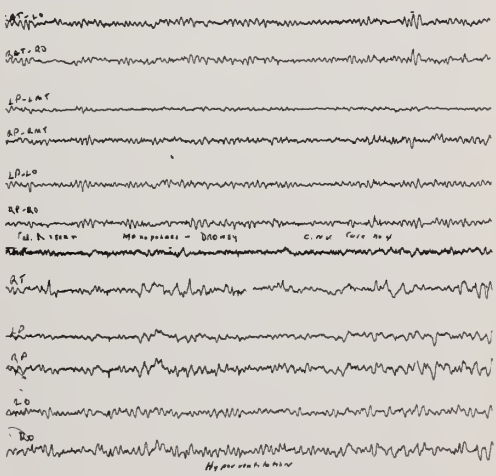


Fig. 3 (Case 4): EEG showing high amplitude, right temporal spike discharges.

Before the electroencephalogram, the patient was treated with analgesics, muscle relaxants and tranquilizers without any success. There was a remission of the headaches with the use of diphenyl hydantoin 100 mgm. t.i.d. Unfortunately the patient failed to keep her last appointment 3 months ago. We were unable to study the other members of the family.

Case 5: This patient is a 34 year-old married female who was seen in consultation with a six-month history of recurrent left-sided headaches. She claims fainting with some of the bouts of headaches but no loss of consciousness and no seizures.

The rest of the personal and past history was

non contributory. The family history failed to reveal any cases of epilepsy, episodic headaches or any other nervous disorders.

The physical and neurological examinations were negative.

The routine laboratory studies, the skull and cervical spine x rays were negative.

A series of electroencephalograms have been performed in this patient. The first one showed asymmetry of the occipital alpha but no seizure discharges. The next two studies showed bilateral synchronized epileptiform discharges consisting of bi-parietal spike activity, and the last one, after treatment with phenobarbital, was normal.

The patient was unable to tolerate diphenyl hydantoin and primidone (mysoline) and was placed on phenobarbital ½ gr. three times daily and 1 gr. at bed time. For the past 10 months she has been completely free of the headaches.

Case 6: This patient is a 32 year-old, married male who gave a history of recurrent episodes of headaches of 5 years duration. Some of the early episodes occurred following periods of watching television. The headache is most frequently localized in the occipital area and is non-pulsating. At times it is associated with nausea and light-headedness.

He was studied in another hospital where skull series, lumbar puncture and pneumography were reported as normal. He was also seen in a psychiatric hospital for a year without relief of the headaches. There was no past history of epilepsy and a negative family history.

The neurological examination reveals congenital strabismus, ataxia on walking in straight line, congenital nystagmus and overactive reflexes on the left.

Routine laboratory studies, blood chemistry, skull series and lumbar puncture were all negative.

Two electroencephalogram showed bitemporal epileptogenic synchronized discharges (Fig. 4). The patient was diagnosed as having multiple congenital defects of the central nervous system and an epileptic disorder.

He was placed on diphenyl-hydantoin and primidone with partial control of the headaches.

Cases 9 to 13 are members of a family suffering

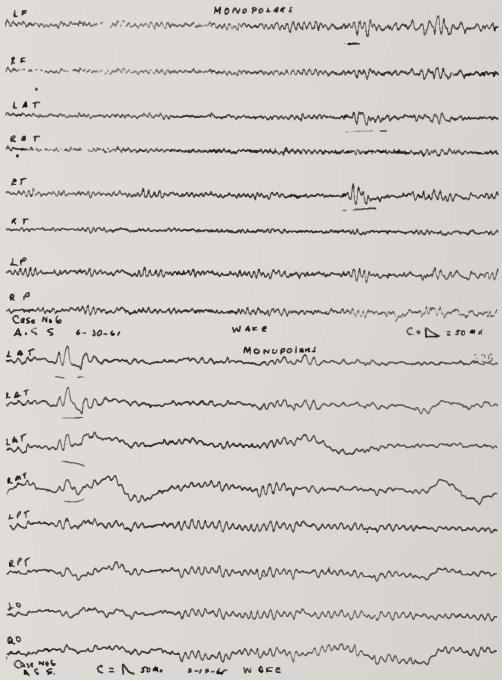


Fig. 4 (Case 6): EEG revealing bitemporal epileptogenic synchronized discharges.

with episodic headaches (Fig. 5).

Case 9: A 33 year-old white female with a history of recurrent headaches for 5 years. The headaches recur frequently following her menstrual period. The headaches will usually start over the occipital area, often radiating to the frontal area bilaterally. They are described as deep and constant, "like a pressure." The patient admits having short episodes of dizziness but no unconsciousness and describes questionable lapses of amnesia that last for seconds.

The past medical history is non-contributory. The family history reveals similar episodes of headaches in several members of the family (Fig) 5.

The physical and neurological examinations were negative. The routine laboratory, skull and spine series were normal.

An electroencephalogram (Fig. 6) showed synchronized epileptiform discharges suggestive of a centroencephalic epileptic disorder.

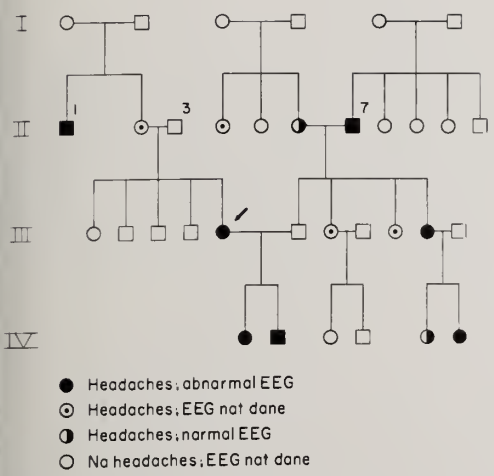


Fig. 5 (Cases 9-13): Pedigree of family of patient with epileptic headaches. Propositus (Case 9) is identified by arrow. Case II - 7 also has epileptic seizures. EEG on Case II - 3 is normal. EEG on Case II - 1 shows low voltage but no seizure discharges.

The patient was treated in the past with ergotamine tartrate, sedation and analgesics without improvement. She was placed on primidone 250 mgm. three times daily with complete remission of her symptomatology.

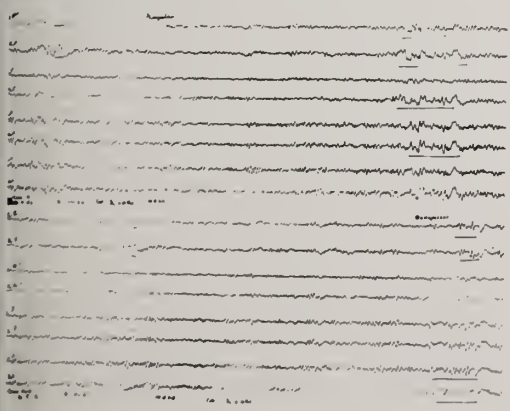


Fig. 6 (Case 9): EEG showing synchronized epileptiform discharges suggestive of a centrocephalic epileptic disorder.

Because of drowsiness the patient discontinued her medication and in 2 days had a recurrence of severe headaches which repeated weekly until she was placed on diphenyl-hydantoin with control of the headaches. At present she has been completely asymptomatic for over 2 years.

See Fig. 7 for the abnormal EEG of this patient's daughter (case 10).

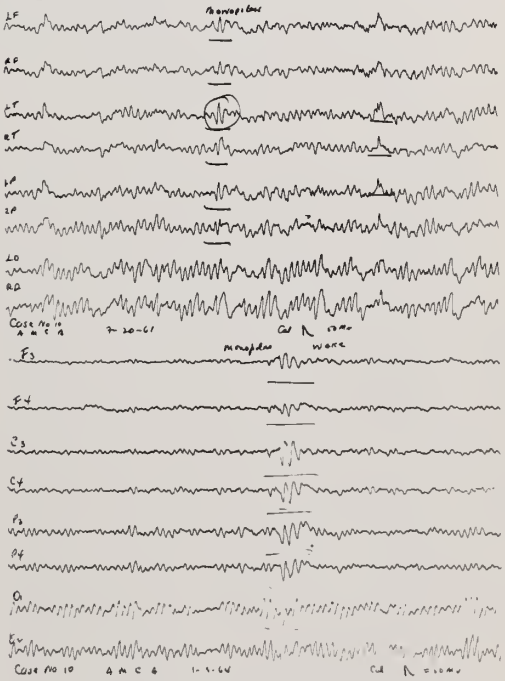


Fig. 7 (Case 10): Abnormal EEG of the daughter in the family showing bilateral synchronized discharges with a tendency of higher amplitude in the left hemisphere.

Tables I and II are a summary of the EEG abnormalities and the incidence of epilepsy in the family history.

Discussion

The possible relationship between migraine and epilepsy has attracted the attention of physicians for many years. Hughlings Jackson, around 1879, thought that migraine could be classified with the epilepsies

TABLE I: SUMMARY OF CASES

Case No.	Sex	Age	Electroencephalographic Findings	Response to Other Therapy	Response to Anticonvulsants	Comments
1	F	38	Bitemporal Epileptiform Activity	None	Good	Epileptic headaches with synchronized EEG abnormality
2	M	17	Synchronized spike, temporals and parietal	None	Good	Epileptic headaches with synchronized EEG abnormality. Family history of epilepsy
3	M	9	Spikes, right occipital	None	Good	Epileptic headaches with focal EEG abnormality Family history of epilepsy
4	F	35	Spikes, right temporal	None	Good	Epileptic headaches with focal EEG abnormality Family history of similar headaches.
5	F	35	Synchronized epileptiform discharges	None	Excellent	Epileptic headaches with synchronized EEG abnormality
6	M	32	Synchronized bitemporal and synchronized generalized epileptiform discharges	None	Fair	Epileptic headaches with synchronized EEG abnormality
7	F	13	Bi-temporal epileptiform discharges	None	Fair	Epileptic headaches with synchronized EEG abnormality
8	M	10	Synchronized epileptiform discharges	None	Fair to poor	Epileptic headaches with synchronized EEG abnormality
9	F	33	Synchronized generalized epileptiform discharges	None	Excellent	Epileptic headaches as a family syndrome, with synchronized EEG abnormality

TABLE II: ELECTROENCEPHALOGRAMS

Number of Cases	Summary of EEG Abnormality	Possible Diagnosis
9	Synchronized epileptiform discharges	Centroencephalic idiopathic epilepsy
2	Bi-temporal epileptiform discharges	Temporal lobe epilepsy
1	Focal temporal	Temporal lobe epilepsy
1	Focal occipital	Focal occipital and/or posterior temporal epilepsy

because it was dependent on "a discharging lesion in some part of the cortex". Gower's (1901), based on his personal clinical observations, considered migraine to be related frequently with the epilepsies.

In 1941, Strauss and Selinsky (2) reported the presence of electroencephalographic abnormalities in 9 out of 20 cases with migraine, in four of which, the abnormality was seen in the headache-free interval. In 5 of these cases there were bursts of 3 to 5 per second potentials after hyperventilation. These bursts could not be obtained in the headache-free interval or after ergotamine tartrate had abolished the headache. The record would continue abnormal if the headache persisted after the injection of ergotamine. This study was followed by the work of Solomon et al (3) in 1953.

Engel, Ferris and Romano (4,5) demonstrated occipital electroencephalographic abnormalities in patients with migraine during the prodrome of scintillating scotomata, prior to the onset of the headache. Following the above original observations, several authors have studied the relationship between migraine and epilepsy and several reports have appeared in the literature (6-13).

The occurrence of non-migrainous headaches as the sole manifestation .of epilepsy was not established until recently and has received less attention in the medical literature. In 1947, Waggoner and Bagchi (14) reported 15 cases with paroxysmal headaches with EEG abnormalities but referred to the cases as "epileptic variants". This paper was followed by observations by Livingston (15), Wallis (16), Heyck and Hess (17) and more recently by Halpern and Bental (18). The latter authors stressed the importance of the use of photic stimulation to precipitate seizure activity in patients with epileptic headaches, thus confirming the previous observations of Heyck and Hess (17).

Our present series of 13 cases is the second largest series to be reported in the literature, if we consider the observations made in the 15 cases of Waggoner and Bagchi (14) as representing instances of epileptic headaches. In our cases the abnormalities recorded in the EEG were definite epileptiform seizure discharges occurring during the headache-free intervals. Photic stimulation was carried out in only 5 of our cases with definite seizure activity appearing in only one instance. The failure to precipitate seizure discharges in the other four instances was interpreted as due to a failure in the technique, since eye

closure was not ordered by the recorder during and at the end of each photic stimulation. In contrast to this observation Halpern and Bental (18), in their 5 cases, were able to demonstrate synchronized spike and slow wave discharges during photic stimulation particularly with eye closure. In two of these cases photic stimulation was the way to prove with certainty the electroencephalographic evidence pointing to an epileptic disorder.

While our intention in preparing this paper has not been to do away with the terms "epileptic equivalents" and "masked epilepsy" because these terms are deeply ingrained in the medical literature, we feel, however, that our series of cases are good evidence that the symptoms observed in these patients form a fairly clear syndrome that should constitute a recognizable clinical entity. Of even greater significance in favor of the concept that we are dealing with a definite clinical entity is the occurrence of this syndrome among direct blood relatives of two of our cases (cases 4 and 9). To our knowledge this is the first report of such an occurrence.

We acknowledge the fact that our series of cases is small but we want to stress the fact that the syndrome would become more commonplace if a greater effort were made to recognize it by means of electroencephalography and all diagnostic means at our command. Besides, the world medical literature, as quoted above, has already provided other examples in favor of this concept, particularly the information concerning the adequate response of these headaches to anticonvulsants, a fact which is in complete agreement with our own observations.

Summary

Thirteen cases suffering with epileptic headaches are reported. Cases 4 and 9 occurred in families with several blood relatives manifesting a similar disorder. Positive findings in the EEG and the response to anticonvulsant therapy are in favor of the epileptic etiology of these cases. The literature concerning the relationship of migraine and epilepsy and with epileptic headache is reviewed.

Resumen

Se informan 13 casos de cefalalgia epiléptica. Se encontraron además varios casos de un desorden similar en las familias de 2 de estos enfermos. Las anormalidades en la electroencefalografía y la respuesta a drogas anticonvulsantes favorecen una etiología epiléptica en estos casos. Se repasa la literatura concerniente a la relación entre migraña y epilepsia y cefalalgia epiléptica.

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ALLERGY TO CULICOIDES FURENS

Presentation of a Case and Immunological Studies

Fernando Machuca, M.D.

In 1955 Arean and Fox (1) reported a case of a severe reaction to the bite of the sandfly, *Culicoides furens.* The genus *Culicoides* is world-wide in distribution and includes many species that are blood sucking pests of man. In the western hemisphere they are commonly known as sandflies, gnats and biting midges; in Spanish as "majes," "jejenes" and "mimes."

Moyer (2) described three cases of papular granuloma annulare due to C. furens stings. The commonest lesion, however is that of papular urticaria. The characteristic lesion is that of a papule with vesicles on top. This becomes excoriated and infected following scratching. The lesion heals leaving a hyperpigmented scar. Itching persists for a long time after the lesion has healed (3).

The following is the report of a case with successful results after hyposensitization. Some immunological studies were performed.

Presented at the 63rd. Annual Meeting of the Puerto Rico Medical Association, November 1965

Case Report

The patient is a thirteen year old girl, first seen on October 17, 1964 with a history of a papular rash in the exposed areas following sandfly stings. Both legs revealed multiple hyperpigmented scars. Several recent papular wheals were present and many lesions were crusted. There were some lesions in the upper extremities as well. The use of insects repellents had been of no help.

The patient was skin tested with a 1-500 W/V whole body saline extract of *C. furens,* giving a four plus reaction. On October, 17, 1964, she was started on hyposensitization with a dose of 0.1 ml of a 1-5000 dilution. The dose was increased by 0.1 ml at weekly intervals. After a relatively short period of treatment, the patient improved. New lesions appeared very infrequently in spite of the fact that the patient is a very active outdoor-type of girl who lives in a endemic area.

Although the patient has improved considerably, the old hyperpigmented scars persist.

Immunological Studies

So far six similarly affected patients have been treated. The case presented is the only one that has received prolonged treatment.

The sera of three of these patients, including the case presented, were obtained prior to treatment. After centrifugation the sera were frozen and kept until used. Serum was again obtained from this case after ten months of treatment.

Passive transfer was performed using the pre-treatment sera. All three gave positive results. Part of the sera was then incubated at 56°C for one hour. Passive transfer using this sera gave negative results. The antibodies transferred are thus thermo-labile.

The sera were then challenged with mosquito (Culex), Caddisfly and cockroach antigen. No reaction occurred. This fact supports the finding of Fox (4) that there is little or no cross-reaction after immunizing rabbits against mosquitoes and sandfly and testing the sera of the immunized animals using the Ouchterlonny agar-gel technique.

Passive transfers were also positive when challenged with heated antigen for one hour at 56°C. Thus the antigen is thermostable, a characteristic shared with only a few antigens.

So far no prescipitin antibodies have been demonstrated using the agar-gel technique.

Discussion

The pathological lesion as described by Fox (1) is that of eosinophilic and neutrophilic infiltration accompanied by monocytes. Acantholysis and hydropic degeneration of the basal layer and degeneration of the basement membrane is present. There is degeneration of collagen fibers, endothelial swelling, perivascular hemorrhage and farther perivascular infiltration by lymphocytes, monocytes and hystiocytes. This picture when seen in man to corresponds to the Arthus reaction in experimental animals.

I have presented evidence showing that the antibodies present in the sera of these three patients are skin-sensitizing, heat labile and species specific. These characteristics suggest that we are dealing with reaginic antibodies.

Loveless (5) and Osgood (6) have reported that precipitating — anaphylactic-type of antibodies are frequently present together with reaginic antibodies in insect allergy. So far we have been unable to demonstrate precipitin antibodies in the sera so far studied.

The prompt clinical response in six patient treated suggest that the mechanism is one of hyposensitization rather than desensitization.

Summary

A case of *Culicoides furens* allergy was presented. Hyposensitization was carried with success. Early treatment is recommended if permanent scaring is to be avoided.

Immunological studies suggest the presence of skin-sensitizing, heat-labile and species specific antibodies. Precipitin antibodies have not been demonstrated as yet. The antigen is heat stable, a characteristic shared with only a few antigens.

Resumen

Se presentó un caso de alergia al *Culicoides furens*. Se trató con éxito por hiposensibilización. Se recomienda tratamiento temprano si se desea evitar cicatrices permanentes.

Los estudios inmunológicos (informados) sugieren la presencia de anticuerpos que sensibilizan la piel, son estables al calor y son específicos en cuanto a especie. No se demostró la presencia de anticuerpos precipi-

tantes. El antigeno es estable al calor, una característica poco común entre los antigenos.

Acknowledgement

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PRESENT POWER POTIONS FOR PESTILENCES AND PLAGUES

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Antimicrobial substances account for 40% of all pharmaceutical sales. All of these agents are poisons in that too little stimulates and too much kills, both microbial and human cells. Each has the unique capacity to interfere with, or alter in some fashion, no more than a single essential function of some organ or microbial population. When given to the human, frequently the balance between the stimulating effect and the killing effect is slim indeed, and when one considers that there are three dozens of such drugs available for prescription, it is an interesting fact that the physician kills more bugs than people. Proper usage of antimicrobial agents requires that the physician have at least two qualities —the capacity to choose (there is nothing perfect where there is no choice) and the ability to choose the best. This report is concerned solely with the second of these qualities. Perhaps some prejudice is to be expressed, but in general there is agreement that for each infectious circumstance there is but one drug which has distinction; in fact, sorting of science from all the marketed garbage really is not too difficult.

The title "Present Power Potions" emphasizes an appropriate adage— ..."learn to forget wisely. He who was able to discern the best yesterday will know how to value rightly today." (1) A potion is a dose of medicine or poison, a draught of a powerful drug for treatment purposes. Antimicrobial agents clearly fit this definition. With uncommon exception the most potent or efficacious therapies for microbial diseases are no more than 30 years old and most are only 20; a few have yet to pass their first anniversary. Although in this three-decade period, many drugs have appeared and have been declared good, it is surely true that most of the highly advertised drugs now deserve to be shelved.

It might be sound if I were to demonstrate in more detail the changing patterns of microbial diseases which are being experienced, (2-7) for such information would enhance the value of this report, but only one table need be shown (Table I). In any event, the newer plagues affecting man and beast are viral, and fungal, and the troublesome pestilences are of gram negative bacterial origins; no longer are pneumococci

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the commonest final friends of the old man, albeit, according to Dr. Austrian, they remain in our society in very great numbers. (7).

Although viral diseases remain our society's worst destroyer of health (but not life)

TABLE I: CHANGING PATTERNS OF PNEUMONIA IN HOSPITALIZED PATIENTS

Etiologic Agent	Percentage (1)		
	1945	1955	1965
Pneumococci	98.	20.	18.
Staphylococci	0.5	18.	12.
Gram negative bacteria	1.0	12.	15.
Viruses	0.5	50.	55.

(1) After Dowling, Reimann, Syracuse experience.

and although these little beasts reduce by a very great deal our days of fun, there is as yet no dependable chemoprophylaxis or chemotherapy for any of them. This statement will be outdated shortly but the advances as depicted (Table II) are yet too

TABLE II: NEW THERAPEUTIC AGENTS AGAINST SOME VIRAL PESTILENCES

Action	Agent
1. Chemical agents that interfere with viral attachment to host cells:	Adamantine
2. Chemical agents that interfere with RNA and DNA synthesis, or viral multiplication:	Iododeoxyuridine Thiosemicarbozones (? poxes)
3. Mainly for prophylaxis	Interferons

new for sensible description. Similarly fungal diseases (or Sam Asper's Ascogoniums, as suggested a year ago (2) are undoubtedly increasing in incidence. They are not treated easily or safely, nor with any more success than several years ago, and they will not be mentioned except in passing.

There are several maladies in man whose causes are more difficult to control, mainly because their most effective antagonists are poisonous to the host (Table III). To be

TABLE III: MICROBIAL PERSISTORS THAT PLAGUE US

Bacteria	Drug
Aerobacter aerogenes	Kanamycin Cephalosporins Polymyxins
Klebsiella pneumoniae	Kanamycin Cephalosporins Streptomycin with Penicillin G
Proteus species	Ampicillin Kanamycin Cephalosporins
Pseudomonas aeruginosa	Polymixins and Gentamycin
Salmonella species	Ampicillin Cephalosporins

sure, the number is shrinking, but the physician treating them must be somewhat more sophisticated and knowledgeably careful in his management of them. They represent the only remaining bacteria that cause human woes which are not simply and safely treated with drugs. All are gram negative, each produces a number of enzymes, like penicillinase, which hydrolize to impotency some of the penicillins, and they are capable often of emerging resistant to their antagonists. There is though a good and a potent treatment for each; all that is required is judg-

ment in prescription.

Table IV lists some of the new chemo-

TABLE IV: NEW AND POTENT POTIONS WITH BRIGHT FUTURES

Drug	Uses
Amantadine (Adamantane)	Some influenzal viruses
Gentamycin	Gram negative microbes, mainly pseudomonas
Cephalosporanic Acids	All Gram positive and many Gram negative microbes
Synthetic Penicillins Hetacillin Cloxacillin Dicloxacillin	All Gram positive and many Gram negative microbes

therapeutic potions that are useful in treatment of these gram negative pests and some others that deserve comment also. Adamantine is a safe synthetic agent with chemoprophylactic and chemotherapeutic activity against at least one virus, but because its potentials and deficiencies are not now well defined, it cannot be discussed sensibly. Were this not so, this discourse would be more exciting.

Cloxacillin (Tegopen ® is now marketed in capsule form; its parenteral preparation is not yet available. Dicloxacillin has two chlorine atoms on the isoxazolyl side chain, rather than the one of cloxacillin, and it will be the next to appear. I am not convinced truly that either preparation is appreciably better than the parent oxacillin (Prostaphlin ®). This last has the singular advantage of being available in multiple dose forms. Cloxacillin is somewhat better absorbed from the gastrointestinal tract than oxacillin and daily dosage can be reduced somewhat, *e.g.* from 3 to 2 grams. When its parenteral preparation becomes available, perhaps both methicillin and oxacillin can be abandoned, if for no other reason than simplicity. Dicloxacillin, when absorbed, produces rather extraordinarily high, even unexpected, blood levels so high in fact that capsules of 125 mgm will be the common dose. Contrariwise, dicloxacillin has the unique disadvantage of passing unaltered through the intestinal tract of an appreciable number of subjects, with essentially no absorption. What causes this in about 15% of the subjects is wholly unknown. Until it is explainable, and avoidable, oxacillin remains our solid choice.

It must be emphasized that every synthetic penicillin is active against all gram positive bacteria and cocci. It is conceivable that they eventually will replace penicillin G and could now, except for their expense. In the acute infection, during the period between obtaining a culture and identification of what is in it, we now often prescribe a synthetic penicillin first, shifting later to penicillin G, if appropriate.

Of more interest are the penicillins which are active against gram negative bacteria. Ampicillin was the first, the next will be hetacillin. I presume Gracian's axiom applies to the drug industry, "...always keep something new in reserve with which to dazzle tomorrow." (8) Anyway, as far as we can determine, the two are quite alike. Penicillin has been known to kill many gram negative bacteria. Its usefulness in practical management of such infections, though, has been restricted because of the large quantities required for maximal efficacy. Following the chemical synthesis and later biologic preparations of 6 amino peni-

cillanic acid, vast numbers of derivatives have undergone trials for their killing actions upon gram negative bacteria. Ampicillin was the first to enjoy the desired characteristics of potency and ease of production. It has achieved a very real place in therapy of a number of such diseases and is now drug of choice for *Hemophilus influenza,* all *Salmonella,* and most *E. Coli* and *Proteus* infections. Unfortunately, it is made inactive by penicillinase such as that produced by the *Aerobacter-Klebsiella* group of microbes and some species of *Proteus; Pyocyaneus* have remained resistant for other reasons. Hetacillin, soon to appear, has the same qualities and limitations.

Many years before their development, another series of antimicrobial agents were studied extensively but only recently has the first of the cephalosporins become available. (9) There are multiple reasons for the 15-year delay, mainly because production difficulties precluded a serviceable product. The first material, cephalothin (Keflin ®) proved its merit in a number of instances in which one or more of the penicillins were not practicable to administer. The main use proved to be in the patient allergic to the penicillins.

Despite my predictions of two years ago, overlapping reactions among them do happen (11). Although the cephalosporins and penicillins have similar chemical nuclei, there is complete immunologic distinction between them. Like methicillin and its successors, the cephalosporanic acids bypass the hydrolyzing effects of penicillinases and amidases and are thus active against organisms which produce them. As is true with ampicillin, their use in gram negative diseases has increased very appreciably, and properly so. The first product, cephalothin, is a tough one to administer. Daily dose must be in the range of 4 grams given parenterally and upon injection it has the very objectionable habit of hurting like a bolus of hot wax. Cephalothin consequently has not attained a popular niche. The new material, cephaloridine, contrariwise, is easy to give, is not irritating, is more powerful on a weight basis and it will have a distinctive use in management of many infectious ailments. (Table V). Like the penicillins

TABLE V: CEPHALORIDINE

Active against all gram positive and many gram negative microbes
No cellular toxicity and non-irritating
Parenteral therapy only
Dose 20-30 mgm/kilo/day
No cross allergy with penicillins

it has no cellular toxicity and its only untoward side reaction will be hypersensitivity. It is potent. We have used it for the successful management of 20 morbid infections, including endocarditis caused by both fecal and viridans streptococci, acute salmonella enteritis, bacteremic pneumococcal pneumonias with two-lobe involvement, pneumococcal pyoarthritis, two-lobed bacteremic klebsiella pneumonias, klebsiella sepsis from the kidney, proteus sepsis arising from the urinary tract and several very acute urinary tract infections caused by coliforms. All of these patients recovered—to be sure, cephaloridine was not the only therapeutic support enjoyed by the patient, but it was the only antimicrobial agent administered to them. Frankly we were and are gratified by these successes, and highly endorse it as a potent

potion for some pestilences, in fact, a great many of them.

Pseudomonas aeruginosa are ubiquitous, are almost as bad a parasite in society as humans, and when invasive are essentially totally immune to the killing effects of common and safe antimicrobial agents. Generally they are non-pathogenic to man, occasionally they discriminate and change careers to become true monsters. This happens predictably when their benign endowments meet with the bad design of a sick or burned man's innate defenses and when other drugs have altered that man's own saphrophytic microbes, leaving him eligible for suffering by the green hordes. Polymyxins B and E have been available for about 10 years they too were first studied almost 20 years ago but proved difficult for practicable production. Polymyxin E or colistin is less toxic than its predecessor and is also on a weight basis, less potent. Consequently, with both, when prescribed in equally effective daily doses, serious damage to cranial and peripheral nerves and to the kidneys can be expected uniformly within a week. Although reasonably efficacious, their use is quite limited to the very urgent infection (Table VI). Gentamycin, on the other hand, has

TABLE VI: GENTAMYCIN (a polypeptide)

Active against *Pseudomonas*
Less nephrotoxic than polymyxins
Parenteral and topical use only
Dose 1-2 mgm/kilo/day

proved a bit safer and is as fit for use against pyocyaneus. (10) It is a polypeptide drug, is allergenic and is nephrotoxic and it will be available commercially soon (Garamycin ® -Schering). In doses of 1- 1.5 mgm per kilogram, daily, parenterally, it has demonstrated potent antipseudomonal activity. We recommend it, with partial enthusiasm only, because of its toxicity. But beggars are hardly choosers. Of interest is its use in badly burned people. With the resurging interest in silver nitrate as the eschar-producing chemical for third degree burns, a combination of the 1/4% silver and gentamycin-inpregnated gauze, pyocyaneus are no longer the feared invaders on skin. As topical therapy and with a 1-mgm/kilo dose daily, the population of pyocyaneus in burns can be contained. Further, because they are not eradicated, other pathogens are indirectly controlled — true microbial antagonism; the pyocyaneus group being the eventual heroes, not the bums. One day soon we all fervently hope there will be better drugs to control pseudomonal disease. When that happy event occurs, essentially every microbe will have an effective and safe to use antagonist. Then will come other microbial kinds of explosions and we will have to become discriminating in other ways and with other things.

There have been reviewed new agents to be used in infectious diseases and a certain philosophy about their prescriptions has been expressed. It seems sensible now to consider a few general theses about antimicrobial therapy (Table VII).

First, no drug alone or in any combination wholly sterilizes any infected lesion. The body must always contribute with its own defensive mechanisms if cure of an infection is to be expected. Actually a drug is used only to tide the patient over until he has had time to mobilize these defenses, such

TABLE VII: THREE AXIOMS

1. No drug sterilizes a lesion. The host must participate for final cure.
2. Adequate drug-bug intimacy is required. Dose of drug need not be altered according to severity of illness.
3. Antimicrobial agents do not alter viral disease except to select which bacteria will superinfect.

as antibody and inflammation. Obviously the prompt and effective prescription of a good drug helps the host in a very real way by reducing appreciably the invading bacterial population, thus easing the job of combating the remaining invaders.

Secondly, efficacy of a drug is measured solely by its speed and degree of killing bacteria. Neither of these attributes can be enhanced by increasing doses above the requisite amounts. The requirement for proper prescription is to provide the patient with a sufficient dose that adequate drug—bug intimacy is achieved. Physiologic and anatomic barriers to distribution of drug into the infected space are the main determinants to size of daily dose, not severity of the clinical illness.

Lastly, routine use of antimicrobial agents in patients with ordinary viral disease (not rickettsia or mycoplasma) will not avoid bacterial superinfection, nor will any alter favorably the course of a viral disease. Contrariwise, use of one or more agents can directly select which resistant bacterial or fungal pathogen will invade the host later. This nullifies in a very real fashion any presumed benefit from so called prophylactic use of an antibacterial agent.

There are more than 30 antimicrobial agents available for use by the physician—and it is evident that few can possibly know how to use each wisely. Nor is it necessary to do so. If the physician would learn to use no more than 8 with propriety, all bacterial diseases would be treated well. Four penicillins-G, ampicillin, oxacillin and cephaloridine; two agents for management of gram negative bacterial diseases-Kanamycin and either polymyxin B or gentamycin; and two broad spectrum agents like tetracycline or a sulfonamide, will treat very well every infection from the common mild ones to the most severe.

The biggest test of a physician's ability to treat well is the decision to prescribe promptly for the patient very morbidly ill with an infection, the precise cause being unknown, and in whom there is no time for laboratory evaluation. These are hospital problems but the physician must decide quickly and correctly. Our selection of crash programs is as follows (Table VIII):

TABLE VIII: THREE "CRASH" ANTIBIOTIC REGIMENS

I. Large doses penicillin G (12 million units daily) plus 1 gram streptomycin

II. Kanamycin 1.5 - 2. grams daily

III. Oxacillin 4 - 6 grams daily plus
II. Kanamycin 1.5 - 2 grams daily
Cephaloridin 3 grams daily

1. In the presence of peritonitis, or empyema, or endocarditis or acute pyoarthritis, the treatment should include 12 million units penicillin G daily, given intravenously or intramuscularly, plus 1 gram streptomycin. It is an exceedingly rare circumstance when more than 12 million units of

G per day are needed.

2. In the presence of urinary tract infection, with septic shock, Kanamycin 0.5 gm, three or four times daily, is superb treatment. This prescription can be continued safely for from 4 to 7 days. Thereafter appropriate adjustments in the regimen can be made, depending upon findings in the laboratory and upon the clinical picture.

3. When the infection is of unknown cause and of unknown focus, a combination of oxacillin, 4 to 6 grams intramucular or intravenous daily, plus either Kanamycin (1.5-2. gms. daily) or cephaloridine (3 grams daily intramuscular) will cover effectively essentially every bacterial cause of severe disease.

One of these three programs can be life saving and perhaps they should be employed more often.

Summarizing plagues and pestilences and potions, I observe many paradoxes. Talent and art and industry and choices no longer necessarily set the proper seal. On the other hand, a few infected lives are saved and in an extraordinarily gratifying manner—endocarditis, staphylococcal pneumonia, meningitis, syphilis, even tuberculosis. I see new and effective and safe drugs being produced in surprising profusion, some of them good. There are all kinds of medical, and surgical, and biologic, and chemical adjuncts for treating associated shock and blood loss and tissue damage. There are declining death rates from infective diseases and probably a lesser incidence of new cases of some kinds of infections in the whole population. There are vaccines and antitoxins galore for biologic prevention of many diseases; and mechanical devices for prophylaxis almost defy imagination. Even chemoprophylaxis is enjoying happy times, as are the producers and sellers of antimicrobial agents. And there is Medicare too.

But all does not come out rosy. Infective diseases are still with us and in a hospital setting at least they are as common and are more challenging than ever. Perhaps only the kinds are different, and the severity and the species, but I suspect more than that. It surely is true that a treatment, even a good one, won't eradicate infections, nor will a prophylactic which acts for only a short period. Furthermore, without true sterilization, or the germ-free state, a phenomenon we probably do not wish to achieve, new, different and stranger eruptions predictably are bound to occur.

It seems to me that the excitement of the past two decades concerning chemotherapy and chemoprophylaxis has delayed the inevitable search for precise reasons as to why a human gets diseased by unthinking, viable things 1/10,000,000th his size.

Finally, I greatly suspect that this venerable and discriminating Association will have yet another discourse on infections in the not too distant future—and another after that—presuming of course that I have not ruined the topic this year. New and multiple potions like dicloxacillin, gentamycin, cephaloridine and adamantine are gorgeous things and they are surely better than the ones available 10 years ago. But they will not prevent new pestilences by viruses and fungi and even bacteria not yet known to have the capacity to have pathogenic careers in man.

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Cases Reports

LEAD POISONING

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Lead poisoning in adults, is essentially of occupational origin. It usually occurs among workers employed in storage-battery plants, smelting plants and many other procedures in which lead is used. Rarely, poisoning may result from ingestion of lead compounds. In children, plumbism usually results from ingestion (1) of readily accessible objects or compounds as paints, toys, and cosmetic powders.

Inorganic lead compounds are absorbed into the body by the alimentary and respiratory tracts. Some organic lead compounds may also be absorbed through the skin.

Even if lead poisoning is rather uncommon in Puerto Rico, it seems worthwhile to describe the case of an adult male showing the representative clinical and laboratory findings of this condition. The commonest expression of plumbism in adults is that of acute abdominal pain that may represent a diagnostic problem and even unnecessary surgical intervention may result if the diagnosis is not considered. We will also present a review of the clinical picture, laboratory findings, pathophysiology and treatment of this condition.

Case Report

This 38 year old white male was seen at the Emergency Room of the University Hospital on April 8, 1965 with a history of severe, colicky, epigastric pain of 24 hours duration. The pain was not relieved by atropine and Demerol given at the local Health Center. It was associated with nausea and vomiting. He also gave a history of anorexia, weakness and a 20 pound weight loss in one month. He denied fever, diarrhea, jaundice, dark urine, melena, hematemesis, or previous episodes of abdominal pain.

At the Emergency Room the patient was seen by the surgical resident who found no evidence of an acute abdomen. Serum amylase, chest x-ray and flat plate of the abdomen were normal. The hemoglobin was 8.0 grams per 100 ml. but there was no evidence of gastrointestinal bleeding. He was referred to the Hematology Section for evaluation of the anemia. A peripheral blood smear showed normochromia and marked basophilic stippling of the red blood cells. A bone marrow revealed a more prominent basophilic stippling of the normoblasts and an iron stain showed increased iron stores, sideroblasts and siderocytes. The diagnosis of lead poisoning was suspected on account of these findings. A qualitative urine test for coproporphyrin III was strongly positive. On detailed questioning the patient stated that for the past 2½ months he had been working breaking up 200 batteries daily to remove the lead to sell it. The patient was then admitted for further management.

Physical examination revealed a blood pressure 120/70, mm Hg pulse 80 min. and temperature 98.6ºF. The patient was a well developed white male looking pale, chronically ill and in acute distress because of abdominal pain. The mucosae were pale. There was no icterus. The tongue was well papillated. A lead line in the gums

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was questionably present. The lungs were clear. The heart was not enlarged but there was a grade 2 soft, non radiating apical systolic murmur. The abdomen was diffusely tender specially in the epigastric region. There was no rebound tenderness and peristalsis was active. No organs or masses were felt. The neurologic examination was normal except for hyperactive deep tendon reflexes.

The BUN was 14 mg.%, hemoglobin 8.2 and 9.4 grams per 100 ml., white blood cell count 6,000 and 7,000 with a normal differential. The urinalysis was normal. Reticulocyte counts ranged from 2.2 to 1.5%. Total proteins were 5.6 grams%, fasting blood sugar 87 mg.%, globulin 1.3 grams%, albumin 4.3 grams%, SGOT 30 units, SGPT 19 units, calcium 7.8 mg.%, phosphorus 3.15 mg.%. Electrolytes and electrocardiogram were normal. No BSP was retained in the serum 45 minutes, of the injection. Blood lead level was reported as 0.269 mg. per cent (normal up to 0.05 mg. per cent).

On admission the patient was started on sodium bicarbonate and milk with slight relief of the pain. He also received atropine, Demerol and Gelusil with only some improvement of the pain. Therapy with calcium disodium Versenate was started one hour after admission. A dose of 1 gram in 500 cc of dextrose in water was given to last 2 hours. Similar doses were administered every 12 hours for a period of 5 days.

A significant improvement in the abdominal pain was noted at the second day of treatment and by the fourth day it had disappeared completely He remained asymptomatic during the rest of his hospital stay. The urinary output was adequate at all times. At the time of discharge (12 days after admission) the anemia was still present but there had been a marked reduction in the basophilic stippling of the red blood cells.

After discharge the patient did not return to his previous job with batteries. He went to New York and was not seen again until August 26, 1965. At that time the hemoglobin was 13.2 grams per cent, reticulocyte count 1.5%, WBC 10,000. Peripheral blood smear showed very slight basophilic. stippling of the red blood cells. Urine test for coproporphyrin III was negative and a repeat blood lead level was 0.04 mg. per cent.

Discussion

The average normal intake of lead in adults is 0.4 mg. per day in food, beverages and respired air. After its absorption it is transported almost exclusively by the red blood cells (2) and distributed in the tissues of the body. About 90% is stored in bones as lead triphosphate and the remainder mostly in the liver and blood. Skeletal lead is normally mobilized very slowly. Removal increases by acceleration of calcium turnover and by chelating agents. Renal excretion of lead depends on renal function and blood concentration. The limited excretion is in part due to its affinity to the red blood cells.

Accumulation of lead in the body occurs when daily intake is over 0.6 mg. daily, usually coincident with abnormal exposure. Systemic manifestation of intoxication may occur after the concentration of lead in the tissues exceeds a critical range but this is not always the case. At times symptoms of intoxication are triggered by obscure factors.

Lead is a protoplasmic poison. It does not produce characteristic changes in the tissues except for the presence of possibly pathognomonic nuclear inclusion bodies in the renal tubules (3) and hepatic cells. However, lesions found include: a) degenerative lesions involving the extensor muscles of the extremities and the associated peripheral nerves, b) cerebral edema with non specific damage to nerve cells, c) basophilic stippling of red blood cell thought to represent precipitated RNA or perhaps abnormal globulin from the altered hemoglobin synthesis, d) perivascular deposits of lead sulfide in submucosal papillae of gums (lead line), e) changes in metaphyseal areas of long bones in children seen as transverse lines of increased density in roentgenograms.

The hematologic alterations seen in plumbism are mostly due to inhibition of heme synthesis (4, 5) Heme is normally synthetized from condensation of activated glycine and succinyl-Co A to form amino-B-keto adipic acid, which then undergoes decarboxilation to form aminolevulinic acid (ALA). Two molecules of ALA in the presence of ALA dehydrase form porphobilinogen (PBG). The biosynthetic pathway from PBG to heme proceeds over a series of porphyrinogens (uro- c o p r o-protoporphyrinogens). Uroporphyrins and coproporphyrins are not in the direct line of hemes synthesis but are, rather, terminal products of side reactions arising by auto oxidation of parent compounds. The final step is the incorporation of iron into protoporphyrin to form the heme molecule. All the main components of this pathway are present normally in urine in minute amounts except protoporphyrin. The latter is found regularly in all human red blood cells in its free form.

Lead inhibits the formation of heme by blocking the production of ALA from glycine and succinate and that of PBG from ALA. It also blocks the incorporation of iron to protoporphyrin. It does not inhibit the iron uptake but its utilization for hemoglobin production. Granules of iron can be shown on electron microscopy in the marrow red cells of patient with plumbism (5). Also iron stains of bone marrow show sideroblasts and siderocytes.

The inhibition of the maturation cycle of hemoglobin by lead results in an increase of certain porphyrins in the circulating blood and urine of which coproporphyrin III is the most significant (6). The increase in urinary coproporphyrin III can be determined by a simple laboratory procedure. It is considered one of the earliest signs of the toxic effects of lead. It can also be increased in the urine by intoxication with other heavy metals, in hepatic disease and in iron deficiency anemia.

ALA concentration is also increased in the urine (7) and it is an early, sensitive indicator of plumbism. Protophorphyrins are increased in circulating red blood cells and can be detected as fluorocytes when blood is examined under the fluorescent microscope (8). Urinary PBG and uroporphyrin are rarely increased in lead poisoning.

The synthesis of globin can also be inhibited (9) by lead and even to a greater extent than that of heme.

Lead can exert a direct effect on red blood cells decreasing their survival, increasing their mechanical and osmotic fragility.

Symptoms and signs of plumbism most frequently involve the gastrointestinal, nervous, and hematopoietic systems. Usually symptoms are more striking than physical findings. In the adult, acute colicky abdominal pain is the usual presenting complaint as occurred in our patient. The mechanism of pain is unknown. It is similar in nature to that of acute porphyria that is also associated with abnormal heme synthesis. Other symptoms include anorexia, weight loss, vomiting, constipation and weakness. The patient looks debilitated and pale. A lead line may or may not be present. The disease is essentially afebrile.

Some patients may present complaints referable chiefly to the neuromuscular system with paresthesias or wrist drop. The cerebral manifestations of the disease may develop suddenly with confusion, headaches, convulsions, disorientation and even deep coma. Lead encephalopathy is the usual present-

ing form of the disease in children but, like adults, they can also show manifestations of plumbism other than encephalopathy. In adults, the picture of encephalopathy is more common when intoxication occurs with tetraethyl lead or when lead is rapidly absorbed as with lead fumes and dust.

The diagnosis of plumbism is made on the basis of clinical manifestations, history of exposure and the abnormal laboratory findings.

The presence of abnormal quantities of lead in blood and urine is the only specific evidence that excessive amounts of lead have been absorbed but is not in itself evidence of lead intoxication unless accompanied by a clinical picture consistent with the disease. The normal blood lead level is up to 0.05 mg. per cent and the urine level up to 0.08 mg. per liter. Our patient had an initial blood lead of 0.269 mg. per cent, that is, about 5 1/2 times greater than normal. The urinary lead was not determined in our patient.

Other non specific but helpful evidence includes the following: 1) presence of transverse lines of metaphyseal density in bones and opaque substances in gastrointestinal tract of children, both detected by roentgenograms, 2) normochromic or slightly hypochromic anemia, 3) reticulocytosis from 2 to 7%, 4) basophilic stippling of red blood cells, 5) increased urinary coproporphyrin III excretion.

Besides the common medical and surgical causes of abdominal pain which may enter in the differential diagnosis of lead intoxication special mention should be made of acute intermittent porphyria (10). Abdominal and neurologic manifestations are common in this disease. The prominent clinical difference between the two diseases is the anemia present in over 90% of the cases of plumbism and in only a small number of cases with porphyria. Acute intermittent porphyria is more common in females. The paresis of lead poisoning is usually of the lower motor neuron type, whereas 10% of the cases of acute porphyria have evidence of upper motor neuron involvement. Hypertension is more common in porphyria although it may also occur in plumbism. In both conditions there is a pronounced increase in urinary excretion of ALA. In most cases of porphyria the excretion of PBG is greatly increased and this is almost pathognomonic of the disease. In lead intoxication there is none or only slight increase in urinary PBG. The urinary coproporphyrin is usually much increased in lead poisoning, and less so in most cases of acute porphyria.

The first important step in the management of lead poisoning is cessation of exposure. This is probably enough in mild cases. In patients in which clinical manifestations are prominent treatment is aimed to relieve symptoms and promote elimination of lead from the body.

Cathartics may be employed to remove lead present in the gastrointestinal tract. Abdominal pain is best treated by the use of intravenous calcium gluconate. The anemia usually does not require any specific treatment.

The only specific treatment for plumbism is by promoting elimination of lead from the body. This is successfully accomplished by the use of chelating agents. This form of therapy does not produce immediate relief of symptoms nor is it life saving when patients are seriously ill since it is not an antidote for the toxic effects of lead. However, it does shorten the duration of the illness by gradual reduction in tissue and

blood levels of lead. Amelioration of symptoms and signs of lead poisoning usually begins 36 to 72 hours after institution of therapy.

The present treatment of choice is the calcium disodium salt of ethylenediaminotetra-acetic acid (calcium disodium Versenate). This drug is available in 5 ml. ampules containing 1 gram of the chelating agent for dilution and intravenous use. This agent combines with metallic ions to form water soluble complexes or chelates. The calcium affinity of ethylediaminetetra-acetic acid (EDTA or Versene) is saturated but still retains its ability to entrap lead since it binds lead more firmly than calcium. Lead replaces calcium and the lead chelate thus formed is readly excreted, virtually undissociated. The absence of free ions of the metal obviates the characteristic toxic actions during the process of excretion. Approximately 80 per cent of the drug is excreted within 2 hours and 95-98 per cent within 6 hours (11).

EDTA is poorly absorbed when given by mouth and is very painful when administered intramuscularly. It is given intravenously in a dose of one gram diluted in 250-500 ml. of saline or dextrose in water twice daily for a period of 5 days. For children, the dose should not exceed 1 gram per pound of weight per day. At the end of the first course of therapy the blood level of lead is determined. If it is still above the normal range another course of 5 days is repeated.

Cases of acute tubular necrosis (12) have been reported with the use of EDTA. The urinary output and blood urea nitrogen should therefore be followed closely during treatment. The patient should receive an adequate fluid intake since this, by itself, may increase the urinary output of lead.

Summary

A case of lead poisoning in an adult is reported. The clinical picture, pathophysiology, laboratory findings and treatment of this condition are reviewed. We emphasize the fact that this diagnosis should be considered in any patient in which abdominal pain presents a diagnostic problem.

Resumen

El envenenamiento con plomo es poco común en Puerto Rico. En el adulto la manifestación más sobresaliente de esta enfermedad es el dolor abdominal severo que muchas veces conduce a una laparotomía innecesaria. Un historial de posible exposición al plomo debe obtenerse en todos los casos de dolor abdominal de etiología desconocida. El diagnóstico es fácil de establecer estudiando las células rojas en el extendido de sangre periferal. midiendo los niveles de plomo sanguíneo y urinario y los niveles de coproporfirina en la orina. El tratamiento con Versenato de calcio disódico produce una mobilización efectiva de plomo de los tejidos y aumenta su excreción urinaria. Queremos enfatizar la importancia de considerar el diagnóstico de envenamiento con plomo en pacientes cuya queja principal es el dolor abdominal especialmente cuando es acompañado por anemia en ausencia de hemorragia.

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Presidential Address

SOCIAL CHANGES AND THE PRACTICE OF MEDICINE

"Everywhere the old order changeth, and happy those who can change with it."
—Sir William Osler, M. D. (1895)

A. *General Sociological Concepts*

Man is the most complex organism living on earth, and human nature is, in a certain way, contradictory. We are conservative, but we desire change; we have the inquisitive instincts to investigate and to pioneer new ways, yet we suspiciously view new changes. However, we are moved by curiosity about the things with which we are not familiar, and a desire to obtain the things we don't have, thus motivating these changes. Generally the change is accepted if the group believes it to be an improvement over existing conditions rather than giving consideration to the future effect. A change in any one of the phases in our society usually affects the others. There has been a tendency over the past several years to make more changes occur quickly than in previous years, thus causing our society to be in a constant state of flux, allowing insufficient time for adequate adjustment to the happenings around us. There is insufficient time for a person to become secure in his role in society, which further increases his sense of insecurity.

In the explanation as to how such social changes occur, the personality promoting them influences a large number. The "social invader" has been described as a person who has an iron determination, disciplined will power, a monolithic zeal, absolute conviction of his ideas, ruthless in their application and, in some cases, ready to lie, cheat or to deceive in order to obtain his goals.

A civilized society is one in which people may think and plan by making use of acquired knowledge. In cultures where in the written language is non-existent, and thus civilization does not exist, there is a homogenous pattern of conduct, already defined by tradition in such a manner as to allow for every little social conflict and the "loneliness" of civilized man has not as yet descended on them. The more advanced a civilization, the more complicated is life; the more we depend on each other, the less freedom of action for the individual. We are no longer pioneers who can satisfy all our own necessities. Now we depend on all those around us, and we are, in a manner of speaking, at their mercy, thereby increasing our sense of insecurity. This also might explain the tendency of many who permit the government to act for them without regard for the ensuing circumstances. It is an unconscious identification with government as a guarantee for security, such as, for example, security of employment, education, housing, old age, and others, which has

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caused the unproportionate growth of bureaucracy, thereby damaging individual freedom and initiative.

There have been numerous social changes during the last century, the most important being industrialization, automation, better education, higher incomes, better housing conditions, greater employment, reduction of distances, population increases, growth of cities, improved personal and environmental health conditions, and many other. The practice of medicine is an integral part of our social system and for that reason it is closely associated with all of these social changes which are constantly occurring. Thus it is most important for each of us as physicians to keep abreast of events and a step ahead of them as much as possible, attempting to direct these changes in the best manner for the benefit of our patients and good medical practice.

B. *Evolution of the Practice of Medicine:*

In order to appreciate these changes, we should look into the evolution of medical practice over the years. This should give us an historically perspective view. From its inception, the medical profession was practiced by the "witch doctor of the tribe," who not only handled the medical needs but the spiritual needs as well of the tribe. Over the years, at the time of Hipocrates, specialization had just begun, and there was a rudimentary difference established between the doctor and the surgeon. From the original Oath of Hipocrates: *"Will not make incisions, not even to a stone, leaving these proceedings to the one practicing that craft."*

During the Middle Ages, came the addition of the third category: the pharmacist. Thus the doctor, the surgeon and the pharmacist were the ones handling the medical needs of people until the eighteenth and the nineteenth centuries. Though there existed separate categories, the doctor was still the most important. He would handle any kind of illness. Should there be a need for an operation, he operated; if he had to prepare his own medicines, he would prepare them; thus handling all of the medical needs of his patients. Under these circumstances, obviously the practice of medicine is observed as a practice involving only the doctor and his patient.

Towards the end of the eighteenth century and the beginning of the 19th century of medical practice, Sir William Osler, the famous physician and unequalled master, left an imprint on our profession, and in the eyes of the general public an image of the doctor as a person of authority and compassion; also the concept that a privileged position carries with it sense of social obligation — Noblesse Oblige.

The general educational level of this era was inadequate and only a small group was able to acquire one. The income level was very low and money and property were in the hands of a small number of people. Medical attention was given as a favor to the public, such as charity, and there was not a great demand for such services. As Dr. William Osler used to say, "nobleness obligates." The general concept was that of a doctor who came from an influential family, with a high social position, and who had sufficient economic means to live independently from the practice of medicine and without economic worries. This reminds us of the parable of the widow in the New Testament, St. Luke, Chapter 21, paragraphs 1, 2, 3, and 4, which reads:

1. "And he looked up, and saw the rich

men casting their gifts into the treasury."

2. "And he saw also a certain poor widow casting in thither two mites."
3. "And he said, Of a truth I say unto you, that this poor widow hath cast in more than they all."
4. "For all these have of their abundance cast in unto the offerings of God: but she of her penury hath cast in all the living that she had."

This was also an age where there was ittle known of illnesses and the treatment f symptoms was left to the medicines avail-ble. Under the circumstances, the doctor eing aware of his limitations could give all hat he had: sympathy, advice, friendship, nderstanding, time for conversation and omprehension. This was the age in which nedicine was an art and not a science.

In an environment when the average erson was poor, with no education, long ours of employment, no entertainment, and oor living conditions, so that a person with ood economic resources, well educated and acticing medicine with no economic worries ould be distinguished from the average with o effort on his part. Therefore, it was com-on that the doctors were the leaders in heir communities.

Then as time passed new scientific dis-overies were made: the microscope was in-ented, microbes were isolated, and there as an emphasis on the etiology of diseases stead of the treatment of symptoms. At-ention was primarily given to diagnoses. A etter knowledge of diseases develops the reventive medicine which started the field f public health. Progress continued and nphasis was given to the existing relation-hip between emotions, the mind and diseases, with the development of the concept of psychosomatic medicine.

We now discover that the scientific advances multiply at a very rapid rate over a period of time. We read of something new every day in the field of medicine, and every day we can learn something new. We have now arrived at what is called the Scientific Age of Medicine. This means that when we give a prescription to a patient we are generally aware of their need and what to do to help them. However, being convinced that we are doing the proper thing tends to make us forget sometimes the art of medicine and that a prescription is not enough and that we should give something more. We need to maintain always that close relationship, both personal and intimate, which exists between the patient and the doctor.

C The Practice of Medicine at the Present Time:

It has been stated that presently the world has three social characteristics: wealth, materialism, secularism. The principal characteristic of the democratic system under which we live is the right of freedom and the economic system of free enterprise. In this environment, and due to social and economic changes that have taken place we also find that the doctor, as an individual, and his patients, as a group, as well as the environment in which he practices medicine, have all changed. These fundamental changes have been happening so fast that if we are not alert we will remain behind.

I should like to discuss these changes and the effect on doctors and the practice of medicine today, fully aware that this is a very complicated and argumentive subject. I should like to point out the most important

factors, in my opinion, as I have seen them and have lived through them here in Puerto Rico.

1. Income Level:

Over the years the level of income in our population has improved and increased. This is due to a better distribution of wealth, to industrialization, better job opportunities, more opportunities for training, as well as many other factors.

2. Education:

It is easier now to acquire an education since there are more schools, more scholarship programs and more opportunities. One can say that if a person is sufficiently intelligent he many become a doctor, independent from his own economic means. As a matter of fact, I believe that now the majority of doctors come from families with moderate or lower incomes, which is he opposite from the last century.

A medical career requires a longer period of time now than previously and the knowledge of medicine is so vast and has become so specialized, that there is a growing tendency towards the development of sub-specialization.

Another effect resulting from this vast improvement in the general education of our population is that patients are better informed and read more. For this reason they demand more information and are more conscious of good medical practice.

3. Scientific Investigation:

This is another field that is developing tremendously and with important results in the practice of medicine such as the increase in the number of doctors in the field of scientific research, reducing the number entering private practice, as well as increasing the number of those working for a salary. Government participation in this area increases yearly.

4. Schools of Medicine:

A tremendous effect has been noted in the practice of medicine by the changes taking place in the faculties of medical schools and their stress on full-time personnel (usually specialists) on salaries. Too, increasing government grants are being made for medical educations and the education of para-medical personnel.

5. Hospitals:

Improvements in hospitals, in their faculties, their facilities, has brought changes in medical practice. Hospitals are becoming the popular place for the practice of medicine. There is a continuous increase in hospital emergency room services, with a resultant increase in doctors' offices in the hospitals or nearby. The important role played by government in grants for construction programs, for nurses' schools, scholarships, etc., as well as regulations, planning and legislation such as the newer types of Medicare, increases daily.

In the past, the medical kit was considered sufficient for the doctor on his medical rounds, but it has become increasingly necessary for him also to have a well-equipped office. Now we are living in an age of necessary construction of well equipped hospitals. With the complexity of medical care increasing daily, this is a factor which cannot be

ignored.

6. Prepaid Medical Insurance:

The development and growth of this newest method of offering medical and hospital services has had a tremendous effect on the practice of medicine. Its development on a basis of hospitalization under the practice of the hospitals and the various medical services under the supervision of doctors have increased the problems. Insurance as now developed for services rendered has resulted in a homogeneous system of payments for doctors. The prepaid medical insurance system, however, is one which best guarantees a better relationship between doctor and patient, with the guarantee of medical services rendered by means of the free enterprise system and its advantages ensuring the best medical attention possible for the patient.

7. Practice of Group Medicine:

This new method is becoming more common, since it is an impossibility to guarantee that a single doctor will be available 24 hours a day, 365 days a year. However, we are obligated to render medical assistance adequately to our patients and this can be accomplished only through a combined effort. This takes different forms, but we believe that as time goes by this will become more and more common. Having more free time is now the general tendency and since the doctor is not an isolated individual but a member of an entire society, it is only natural for him to react to the changes in that society.

Other important effects of group practice of medicine ensure a better utilization of facilities, as well as administrative and para-medical personnel. Good medical care can now be given each patient in a more efficient and less exepnsive manner.

8. Growth of Discipline Aids:

Along with the progress in medicine we note an increase in the number of discipline aids that have developed: dietitians, social workers, X-ray technicians, laboratory technicians, technicians in pathology, physicians, specialized nurses, physiotherapists, hospital administration, attorneys specializing in medical problems, sociologists interested in medicine, etc., adding to an increasing list of technicians daily. Since there are many who have legitimate interests in the rendering of such services, it is our obligation to maintain leadership in these fields or the vacuum will be filled by these outside groups.

9. The Government:

From the foregoing we can note that the government is assuming a greater and greater role, actively and directly in medical and hospital services. This may be explained partially by the sense of security provided by the government combined with the erroneous idea that whatever given by the government is gratis, when the truth is that it is probably more expensive than it would be if offered by private sources. The idea, too, has been generalized that the political party which offers more to the people is the one which gets the most votes, again without thinking that the money comes from the taxpayer.

I have already explained that the patient

has changed, now being better educated, with higher incomes, and therefore more demanding of services.

The doctor has also changed, being older at the beginning of practice, and having undergone economic sacrifice for many years in order to finish his career, he usually depends exclusively on his profession for a livelihood.

The environment has also changed and the doctor discovers that the practice of medicine is not an independent one, but that it is influenced by government, prepaid medical insurance, hospitals, schools of medicine, other discipline aids, and group practice.

D. The Big Challenge:

We now come to the big challenge in our profession at the present time due to social evolutions taking place which have already been discussed, so that what was easy previously now is increasingly difficult; what was the usual and accepted role previously is no longer the case; what might have been handed out on a silver platter now has to be worked for. This is now our big challenge.

Previously the doctor was automatically the leader in everything concerning the field of medicine as well as automatically a leader in the civil and political fields of his community. This is no longer the case, and a tremendous amount of work has to be done to become a leader with the thought that if we do not become the leaders others will fill the void and take the leadership.

Knowing the medical profession as I know it, I realize that this big challenge we face presently with its many social changes will stimulate us to do what is expected of us even though it will require more work and sacrifices on our part. We must remain the leaders in the practice of medicine, in the civil field of our communities and in the political forum of our government. Only upon the assumption of all of these responsibilities will we then fulfill our reason to be, which is that our patients will receive the finest medical attention and hospital care possible within our economic means.

Egidio S. Colón Rivera, M.D.
President

EDITORIAL

PROGRESO Y PROPOSITOS

Al terminar un año y comenzar uno nuevo es tradicional evaluar el fruto de la tarea llevada a cabo y trazar nuevas metas para el futuro.

El año 1965 fue uno de importantes logros para el Boletín. Bajo el hábil liderato de nuestro predecesor, un entusiasta grupo de colaboradores en la Junta Editora obtuvo considerable progreso en muchos de los objetivos que se había propuesto.

El crecimiento del Boletín como revista científica ha sido evidente. Testigo de esto es el número de artículos originales publicados, que en el 1965 fue el doble de los impresos en 1962. Una creciente proporción de estos trabajos es de autores locales. Este aumento es, sin duda, sintomático del ímpetu que comienza a tomar en nuestro medio la investigación médico-científica. La proporción de la producción científica que venga a nutrir nuestro Boletín depende en gran parte de cuán eficaz es éste como instrumento para la divulgación de material científico. En relación con esto, es importante anotar que se ha hecho llegar nuestro Boletín a los más importantes centros de enseñanza e investigación de Norte y Sur América y de Europa.

Otro de los adelantos importantes del año que termina fue el cambio radical realizado en la calidad de nuestra imprenta y en el formato del Boletín. Al personal de Talleres Gráficos Interamericanos, que ha dado su entusiasta cooperación a la Junta Editora, corresponde una buena parte del crédito.

Reconociendo los logros, no podemos, sin embargo, olvidar que quedan problemas por resolver y mejoras a hacerse. Uno de estos problemas es la falta de facilidades más adecuadas para llevar a cabo la labor administrativa del Boletín. Por razones económicas, y de espacio no ha sido posible realizar esta labor con la máxima eficiencia. Vislumbramos, sin embargo, progreso también en esta dirección.

Por diversas razones el Boletín no ha llegado a llenar algunas de las funciones que en nuestra opinión le corresponden. Al crear las secciones de Noticias y de Cartas, se ha tratado de asumir parte de la función natural de nuestra única publicación médica como órgano de información sobre diversos asuntos de interés a los médicos. Nos proponemos estimular este desarrollo. Esto no sólo para la Asociación y sus miembros, sino para otras agrupaciones aliadas.

A nombre de la Junta Editora, pido a nuestros colaboradores, lectores y amigos su cooperación, sus críticas y sus sugerencias, para que podamos encauzar el continuado crecimiento del Boletín a la par de las otras actividades médicas del país.

Julio V. Rivera, M.D.

ACTUALIDADES MEDICAS

CURRENT STATUS OF MEASLES VACCINE AND MEASLES VACCINE SCHEDULES*

Progress Report and Recommendation, April 1965

The rapid increase in knowledge concerning the newly available products employed in the prevention of measles warrants a review of current recommendations. The U. S. Public Health Service Advisory Committee on Immunization Practice has recently issued a statement *(Morbidity and Mortality Weekly Reports,* 14:64 (February 20, 1965) which is reproduced below in full. The Committee on the Control of Infectious Diseases of the American Academy of Pediatrics (Red Book Committee) has reviewed the statement and endorses the recommendations contained therein.

The development period of measles vaccine is now over and measles vaccine should be administered routinely to all children without a history of clinical measles or measles vaccination. Immunization against measles is particularly recommended for certain children in high risk groups who are especially prone to develop serious complications. Specifically, these include children in institutions, and those with heart disease, cystic fibrosis, tuberculosis, asthma, and other chronic pulmonary disease. Children with altered immune response (e.g., leukemia, steroid therapy, irradiation, alkylating agents, and antimetabolites) should receive inactivated vaccine.

Five acceptable immunization schedules are available, as outlined in the table on page 38. Of the five, schedules 2 and 3 are most commonly employed, because they confer maximal protection of prolonged duration with the least number of injections. Schedule 5 shows great promise for immunization of infants under the age of 12 months. Live virus vaccines should not ordinarily be administered to children of less than 12 months of age, because of trace amounts of residual maternal antibody which may interfere with antibody response. However, in high risk situations, live vaccine may be administered as early as nine months of age. The inactivated vaccine may be begun at any age.

The facts that live measles vaccine virus does not spread to contacts and that a percentage of recipients develop a significant illness have been cited as evidence against the need for mass community immunization programs in the United States. Immunization should be carried out routinely as an integrated part of the total prophylactic program of each infant.

Measles can be the next infectious disease to be eliminated from the United States if the presently available vaccines are widely used. The vaccines are safe and effective, production problems have been solved, and six competitive vaccines are now commercially available and are approved and licensed

**Reproduced with permission from the Newsletter of the American Academy of Pediatrics of May 1965.*

by the Division of Biologics Standards of the U. S. Public Health Service. Since the initial introduction of poliovaccines ten years ago, there has been a 99.75 per cent reduction in paralytic disease. A similar record may not be attainable with measles, but complete elimination, nevertheless, should be the goal. Measles is now a preventable disease, including all severe complications. To eliminate it we need only take the last step in the long chain of events which leads eventually to the control of an infectious disease, i.e., public acceptance and use of the vaccines now available. We believe the public is ready to accept prevention of measless by prophylactic immunization and we urge all physicians and public health personnel to take whatever steps are necessary to see that all susceptible children receive measles vaccine. Vigorous endorsement and execution of this aim by physicians and responsible authorities should eliminate measles by 1970. A suitable motto for the five-year period might well be "Mortus a morbilli."

Committee on Control of Infectious Diseases

Lewis L. Coriell, *Chairman,* Floyd W. Denny Jr., Dorothy Horstmann, David Karzon, Frederick Robbins, Margaret H. D. Smith, Henry B. Strenge, Franklin H. Top, Robert Ward, Clarence H. Weeb

RECOMMENDATION ON MEASLES VACCINES
By Public Health Service Advisory Committee On Immunization Practice

A. Live Attenuated Measles Virus Vaccine (Edmonston Strain)

Developed in the laboratory of Dr. John Enders, this vaccine, prepared in chick embryo tissue cultures, was first tested in 1958 and since has been given to several million persons in the United States, either alone or in combination with gamma globulin. The vaccine produces in the recipient a mild or inapparent, non-communicable infection which induces active immunity. Although in the majority the symptoms are minimal, approximately 30-40 percent experience fever of 103°F (rectal) or greater, beginning about the sixth day and lasting two to five days. However, even those with high fever may experience relatively little disability and minimal toxicity. In 30 to 60 percent a modified measles rash is seen which begins with or after the subsidence of fever. A few develop mild cough, coryza and Koplik spots.

An antibody response equivalent to that seen in regular measles develops in over 95 percent of susceptible children. Measured as late as four years later antibody levels induced by the vaccine have demonstrated a stability equivalent to that following the natural disease. Protection upon exposure to measles has been noted for at least four years after vaccination.

If standardized Measles Immune Globulin is given in the recommended dose at the same time as the live attenuated vaccine, but at a different site and with a separate syringe, clinical reactions to the vaccine are sharply reduced. About 15 percent demonstrate fever over 103°F (rectal) ; the duration of fever is shortened and the incidence of rash is markedly reduced. Although the frequency of serological conversion is the same as that following live attenuated vaccine alone, the level of induced antibody attained appears to be slightly decreased. Antibody titers have been shown to persist for at least three years and protection against the naturally occurring disease has been noted for at

least two years.

To date, there have been no reports of encephalitis or other serious reactions following administration of the live attenuated vaccine to normal children. A few instances of convulsions, apparently of the febrile type and without known sequelae, have been recorded.

B. Inactivated Measles Virus Vaccine

The inactivated vaccine is composed of attenuated Edmonston strain measles virus propagated on monkey kidney or chick embryo tissue culture, and subsequently inactivated, concentrated and precipitated. The vaccine has been customarily administered, in field trials, in a three dose schedule at monthly intervals. Reactions to the vaccine are no more frequent than those seen after administration of alum precipitated products, such as diphtheria and tetanus toxoids.

Serological conversion after three monthly doses of inactivated vaccine is induced in 90 percent or more of susceptible children. Antibody titers, however, are distinctly lower than those following the live vaccine and in most cases decline to undetectable levels over the following year. These children, although without detectable antibody, demonstrate a booster response when given a fourth dose of vaccine.

Under the conditions of natural challenge, the vaccine has demonstrated an efficacy of between 80 and 95 percent during the immediate six months following administration. A year after administration, the level of efficacy in control trials has been shown to decline to between 65 and 75 percent. Field trials employing a fourth or booster dose have not been reported.

C. Combination Schedules Employing Inactivated and Live Attenuated Virus Vaccines

If live attenuated vaccine is administered one to three months after one or two doses of inactivated vaccine, clinical reactions caused by the live vaccine are sharply reduced; resultant antibody titers are boosted over those produced by the inactivated vaccine alone and appear to be equivalent to those observed following the administration of live vaccine. About 10 percent demonstrate fevers over 103°F (rectal); rash, cough and coryza are rarely observed. Serological conversion occurs in 95 percent given this combination; antibody has been shown to persist for at least 14 months in 90 percent of this group.

Under natural challenge, this combination has demonstrated an efficacy of over 97 percent during a period of 14 months following administration. Although the protective effect of this vaccine combination probably persists beyond this time, substantiating data are not yet available.

Infants given inactivated vaccine in three monthly doses beginning as early as one month of age followed by live vaccine at 12 months of age also demonstrate shaply reduced clinical reactions following the live vaccine. About 5 percent demonstrate fever over 103°F (rectal); rash, cough and coryza are rarely observed. Serological conversion following the live vaccine occurs in over 95 percent. The duration of immunity, as measured by natural challenge or persistence of antibodies, has not yet been assessed in the infant group.

D. Recommendations for Vaccine Use

1) Age

Virtually all children will, at some time,

have clinically evident measles. Marked by severe constitutional symptoms and a seven to fourteen day course, the disease is of additional concern because of secondary complications such as bronchopneumonia and encephalitis. The vast majority of cases of measles occur among those under 15 years of age, particularly those aged 2 to 6 years; only occasionally do cases occur among adults

Vaccine use then is indicated primarily for children The live virus vaccine should be administered only to those *at least twelve months of age* since residual and maternal antibody may interfere with a response among those younger. The inactivated vaccine may be given at any age. Vaccination of adults is rarely indicated since all but a very small percentage, by history, have experienced the disease. Limited data indicate that in the adult, reactions to the vaccine approximate those seen in children.

2) High Risk Groups

Immunizaion against measles in recommended particularly for those especially prone to develop serious complication should they acquire natural measles infection. Specifically, these include children in institutions and those wth cystic fibrosis, tuberculosis, heart disease, asthma and other chronic pulmonary diseases.

3) Prevention of Natural Measles Following Exposure

Limited studies reported to date indicate that there is no protective effect conferred by either vaccine when given *after* exposure to the natural disease. However, live attenuated vaccine administered only a few days *previous* to exposure appears to confer substantial protection.

4) Community Programs

Rarely would there appear to be a need in the United States for mass community immunization programs. Immunization should be carried out as indicated by private practitioners and through established public health programs. Particular attention must be given to programs directed at children in lower socioeconomic areas, since attendance of this group at the usual well child conferences beyond 6 months of age is particularly poor.

E. Dosage Schedules

Four different dosage schedules can be considered for use at the present time in the United States. (See table p. 38)

F. Contraindications to Use of the Vaccines

Parenthetically, it should be noted that neither the live nor the inactivated vaccines contain penicillin.

1) Live Attenuated Vaccine

*a) Pregnancy

*b) Leukemia, lymphomas and other generalized malignancies.

*c) Therapy which depresses resistance such as steroids, irradiation, alkylating agents and antimetabolites.

*d) Severe febrile illness.

*Although there are no reports of unusual complications in any of these conditions excepting leukemia, it is conceivable on theoretical grounds that potentiation of the attenuated disease might occur or, in the case of pregnancy, that damage of the fetus might result. Accordingly, if immunization is indicated, the inactivated vaccine should

DOSAGE SCHEDULES FOR MEASLES VACCINES

Schedule	Type of Vaccine	Age	Doses* and Administration	Comment
1	Live, Attenuated Vaccine	12 months and older	1	Although the live, attenuated vaccine may be administered safely with or without the simultaneous administration of Measles Immune Globulin, most physicians will wish to use the two combined because of the lessened frequency of clinical reactions.
2	Live, Attenuated Vaccine plus Measles Immune Globulin	12 months and older	1 plus Measles Immune Globulin (.01 cc per pound at different site with different syringe)	The live attenuated vaccine should be administered only to those 12 months of age or older since residual material antibody may interfere with a satisfactory response among younger children.
3	Live, "Further Attenuated Vaccine"	12 months and older	1	Clinical reactions following the "Further Attenuated Vaccine" are relatively infrequent; Measles Immune Globulin is not necessary with this Vaccine.
4	Inactivated Vaccine	Any Age	3** (monthly intervals) plus a booster dose after one year	In view of the rapid fall-off in antibody and evidence of decreasing immunity following a primary immunization series, use of this vaccine is not preferred except for special groups in which live attenuated vaccine is contraindicated. The degree and duration of protection which might be afforded to those given a booster has not yet been determined.
5	Inactivated Vaccine followed by Live, Attenuated Vaccine	12 months and older	1 dose inactivated vaccine followed in 1 to 3 months by 1 dose live attenuated vaccine	The preceding administration of inactivated vaccine serves to reduce the frequency and severity of clinical reactions following live attenuated vaccine administration.

DOSAGE SCHEDULES FOR MEASLES VACCINES (concluded)

Schedule	Type of Vaccine	Age	Doses* and Administration	Comment
		Under 12 months	3 doses inactivated vaccine at monthly intervals followed by 1 dose live attenuated vaccine at 12 months of age or older.	The live attenuated vaccine should be administered only to those 12 months of age or older since residual maternal antibody may interfere with a satisfactory response among younger children.

**Manufacturers' directions regarding volume of dose should be followed.*

***In view of rapidly declining antibody levels and protection, at least one booster dose about a year later is necessary. Data are not yet available to indicate when or with what frequency additional booster doses might be required.*

be used.

e) Recent Gamma Globulin Administration.

If more than .01 cc/lb. of gamma globulin has been administered within the preceding 6 weeks, immunization should be deferred since the administered globulin may block the vaccine take.

f) Marked Egg Hypersensitivity

Since the virus is grown in chick embryo tissue culture, the vaccine probably should not be administered to extremely allergic children as indicated by their inability to eat eggs or egg products.

2) Inactivated Vaccine

Either monkey kidney or chick embryo tissue culture may be employed for inactivated vaccine production. (This will vary according to the manufacturer.) If chick embryo tissue culture material has been used precautions (as above) should be taken for possible marked egg sensitivity.

No other contraindications are known.

G. Continuated Surveillance

Although several million children in the United States have received the vaccines without serious complications, continuing careful surveillance for significant adverse reactions is of the utmost importance. It is important that any serious reactions be carefully evaluated and reported in detail to local and State health officials. The Communicable Disease Center will maintain a close surveillance of all such cases.

ADDENDUM

Further Attenuated Live Measles Virus Vaccine

A further attenuated variant of the ori-

ginal Edmonston strain vaccine has been developed by Dr. Anton Schwarz and licensed in February, 1965. This strain was derived by multiple additional passages of the Edmonston strain in chick embryo tissue culture at lowered incubation temperatures.

As with the Edmonston strain attenuated measles vaccine, this further attenuated variant produces in the recipient a mild or inapparent, non-communicable infection which induces active immunity in almost all susceptible children to whom it is administered. In initial comparative studies, the frequency of febrile and exanthematous symptoms accompanying this infection have been shown to approximate or perhaps to be slightly less frequent than those observed in individuals who have received the Edmonston strain vaccine with Measles Immune Globulin. Thus, approximately 5 to 15 percent of individuals experience fever of 103°F. (rectal) or greater beginning about the sixth or seventh day and lasting one to five days; approximately 5 to 15 percent exhibit an exanthem which is less extensive and prolonged in duration than that observed in natural measles. No serious complications have been observed.

The level of hemagglutination-inhibition antibody titers induced by this vaccine appear to be comparable to those achieved following administration of the Edmonston strain vaccine. Persistence of this antibody for at least two years has been demonstrated. Observations pertaining to the duration of immunity under circumstances of natural challenge have not been reported.

Indications and contraindications for use of this vaccine are essentially the same as those applicable to the Edmonston strain vaccine.

SMOKING OF TABACCO IN CIGARETTES*

Smoking of tabacco in cigarettes is clearly related to the induction of lung cancer and brings about other serious cytologic and emphysematous changes in the respiratory tract and induces detrimental changes in the cardiovascular system. Deleterious effects from cigarette smoking are directly related to both the intensity and the duration of smoking. A majority of individuals, acquire the habit of smoking during childhood or adolescence; therefore, individuals acquiring the habit at this time in life undertake the greatest risk to health. The American Academy of Pediatrics should join other health agencies and the Surgeon General of the United States in every effort to discourage acquisition of the habit of cigarette smoking during childhood and adolescence.

Each member of the Academy should be supplied with information exposing the problem and should be expected, as a part of his preventive medical care, to raise the question with older children and adolescents and their parents. Because of the strong bond of friendship usually present between the pediatrician and the parents and children in the families he serves, his counsel and advice might be far more readily accepted than that of any other individual. The pediatrician also should be expected to take leadership or join with other physician in-school and community programs to discourage cigarette smoking.

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José E. Sifontes, M.D., *Chairman*
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THE RUBELLA SYNDROME IN INFANTS*

A Contagious Disease

For more than 20 years it has been known that when a woman contracts rubella early in pregnancy fetal malformations may occur; consisting of all or some of the following: microcephaly, mental retardation, deaf-mutism, cataracts, and anomalies of the heart and great vessels. This constellation of congenital malformations has been termed the rubella syndrome.

Recent studies from several centers have demonstrated that infants may also be born with *active* rubella and may manifest any of the following additional abnormalities: growth retardation (stunting) at birth, encephalitis, glaucoma, hepatosplenomegaly, regurgitative jaundice, thrombocytopenia, purpura, and lesions of the long bones.

Rubella virus may be recovered at birth from a high percentage of such infants born with active rubella infection. The virus has been isolated repeatedly from throat and occasionally from rectal swabs and/or urine specimens of infants up to several months and in one instance, as long as nine months after birth. The usual duration of virus shedding is not fully known, but there is evidence of a diminishing incidence over the first six months. These virus-excreting infants have been documented to be the origin of secondary cases of rubella infection in several instances, largely among hospital personnel.

In view of these observations, it is recommended that infants born with clinical features characteristic of intrauterine rubella infection be managed with the same isolation precautions employed for patients with rubella. It is obviously most important for women in the first trimester of pregnancy to avoid contact with these infants. As a consequence of the major outbreak of rubella in the United States in the winter and spring months of 1964, the problem of management of such infants has attained significant proportions at the present time.

Committee on Control of Infectious Diseases

Lewis L. Coriell, M.D., *Chairman*, Floyd W. Denny, Jr., M.D., Dorothy Horstmann, M.D., David Karzon, M.D., Frederick Robbins, M.D., Margaret H. D. Smith, M.D., Henry B. Strenge, M.D., Franklin H. Top, M.D., Robert Ward, M.D., Clarence H. Webb, M.D.

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NOTICIAS

Locales

PLAZAS PARA MEDICOS

Nos informa el Comandante del Armed Forces Examining and Induction Station que existen vacantes en esa dependencia del Ejército para médicos (fee basis).

Para información adicional los interesados deben ponerse en contacto con Dale D. Bergsten, Captain, Infantry Commanding Armed Forces Examining and Induction Station.

RESIDENCIA EN MEDICINA INTERNA

El Dr. J. Chaves-Estrada informa que existen vacantes para residentes de primero y segundo año en medicina interna en el Hospital de Veteranos de San Juan. Este programa está acreditado por el "American Board of Internal Medicine" y es supervisado por el Comité del Decano de la Escuela de Medicina de la Universidad de Puerto Rico. El estipendio anual es de $4,541 a $5,381.

El Gobierno Estatal acepta esta residencia como equivalente a los servicios requeridos por los contratos firmados al otorgarse las becas para estudios de medicina.

Para más informes diríjase al Dr. Elí A. Ramírez, Jefe, Servicio de Medicina, Hospital de Veteranos, Ponce de León 520, San Juan, P.R.

CONVENCIONES

Enero 21-23, 1966 — Convención Anual de la Sociedad Médica del Distrito Occidental.

Feb. 22-26, 1966 — Convención Anual del Capítulo de P.R. del Colegio Americano de Cirujanos

Abril 25-29, 1966 — Primer Congreso de Medicina Física y Rehabilitación del Caribe, Hotel San Juan, San Juan, P.R.

PREMIOS DOME LABORATORIES

Dome Laboratories, anteriormente Dome Chemicals, Inc., de Nueva York ha establecido por intermedio del Colegio Ibero Latinoamericano de Dermatología (CILAD), dos premios de 800 dólares el primero 400 dólares el segundo para los mejores trabajos originales de investigación no publicados previamente y relativos a algún aspecto fundamental de la dermatología. Se otorgará además diploma y medalla a todos los firmantes de los trabajos premiados.

Los trabajos deben ser escritos en Idioma Español o Portugués.

Los trabajos para optar al premio deben ser presentados al VI Congreso Ibero Latinoamericano de Dermatología.

Este primer concurso se cerrará el 31 de octubre de 1966.

Para informes más detallados sobre las condiciones del concurso, favor escribir a:

Dr. David Grinspan
Arenales 947 - 2o. A
Buenos Aires, Argentina

Nacionales

GROUP PRACTICE

The American Medical Association has published a booklet entitled Group Practice, Guidelines to Forming or Joining a Medical Group. Any physician interested in having this booklet can write to:

Mr. John A. Rowland
American Medical Association
535 North Dearborn Street
Chicago, Illinois 60610

PROJECT VIET-NAM

In response to an urgent appeal to American Medicine by President Lyndon B. Johnson, the American Medical Association is assisting the newly formed voluntary organization known as PROJECT VIET-NAM. This Project, administered by The People-to-People Health Foundation, Inc., is a cooperative medical effort of America's inter-voluntary agencies for the people of South Viet-Nam. The Agency for International Development (AID) is also participating in this program that appears vital to our success in the present crisis in Asia.

PROJECT VIET-NAM was developed to help alleviate the problem of the critical shortage of physicians in South Viet-Nam —a problem that is crippling and demoralizing the civilian population of the country. The matter is of concern to all physicians— those believing that human life everywhere is sacred, and those sharing a stake in the security of the United States. The American Medical Association, cooperating with the President's request, is appealing to each County and State Society for participation in a program that will assist in the procurement of volunteer physicians for this important venture.

PROJECT VIET-NAM will send teams of twenty (20) physicians into Viet-Nam for periods of just *sixty (60)* days. The teams will be divided into four groups, each being assigned to a hospital now being operated under the AID program. Facilities and supporting personnel are available at each installation for carrying out services in accordance with acceptable professional standards. While ultimately many disciplines of medicine may be required, the immediate need is for physicians in *general practice, general surgery* and *orthopedic surgery*. Although service with PROJECT VIET-NAM is on a volunteer basis, transportation from home and return via commercial airline, a nominal per diem, housing, meals and other needs will be supplied. The federal government has also given assurance that all volunteers will be granted the same privileges, courtesies and priority provided government personnel in the area.

Interested physicians may obtain further information and application forms by communicating with:

PROJECT VIET-NAM
2233 Wisconsin Avenue, N.W.
Washington, D.C. 20007
Phone: 338-5730 or 338-6110

HOSPITALS AS EDUCATIONAL INSTITUTIONS

Approved by American Hospital Association
November 17-19, 1965

Hospitals are an essential element in the education of medical and paramedical students and the quality and discipline of patient care has benefitted greatly from the stimulus of the educational regimen in hospitals.

It is clear that those institutions that require the services of the graduates of the educational process must establish the levels of skill to be expected in those who have completed training. Based upon such determination, those responsible for the service function must influence the body of knowledge that is communicated during the course of an education program. This is an inherent right and responsibility vested in the governing authority and executive officer of any hospital sponsoring, supporting, or conducting teaching programs.

At the same time, service oriented forces cannot presume to wield complete control over the educational process to the extent of dictating exact content, relative course values, or pedagogical methods. These must be the responsibility of those doing the educating and must surely include evaluation of the educational worth of practical experience acquired in the hospital environment. This latter is of particular importance because the professions involved must be practiced to be learned, and this practical phase must at the same time satisfy the requirements of true learning and correlate with and give support to the medical care plan of the patient. Both conditions must be met by all programs for all students.

We are of the firm opinion that where these fundamental principles are observed, hospitals are educational institutions in every sense of that term. They should be encouraged to expand this responsibility in order to take their rightful places in the ranks of establishments of learning to which the youth of the nation may confidently turn for their life's work.

NEW PUBLICATION

A Study of Hospital Central Medical and Surgical Supply Services is a new publication released today by the Division of Hospital and Medical Facilities, Public Health Service, U.S. Department of Health, Education, and Welfare.

The publication reports current practices in organizing and operating this rapidly developing service in hospitals.

The study, conducted by Mrs. Marie M. Lech. hospital nurse consultant to the Division, was limited to non-Federal short-term general hospitals. While the services performed by the CMSSS in the reporting hospitals varied widely, generally they included collecting, receiving, processing, storage, inventory control, issuing and distribution of supplies and equipment to all departments that render patient care.

Assistant Surgeon General Harald M. Graning, Chief of the Division of Hospital and Medical Facilities, said the study had been made in response to urgent needs expressed by hospitals.

"Hospital administrators recognize the CMSSS as one of the most important service departments in the hospital," Dr. Graning said. "Yet, no uniformity exists among hospitals in defining the functions of this department, providing adequate facilities with modern equipment, applying techniques of methods improvement, and carefully selecting and training staff."

Adding that the CMSSS is a vital factor in providing improved patient care, Dr. Graning said that the study is the second of a series of Public Health Service publications featuring this hospital service. Additional volumes are being developed relating to procedures, administration, organization, and design.

Authors of the new PHS booklet are Mrs. Lech; Mrs. Ella H. Davis, statistical assistant to the Division of Hospital and Medical Facilities; and John R. McGibony, M.D., former Chief of intramural Research for the Division, who recently retired from the Public Health Service.

The study, Public Health Service P ıblication Number 930-C-10, may be purchased from the Superintendent of Documents, U.S. Government Printing Office, Washington, D.C. 20402, at 30 cents per copy. Free single copies are available from the Division of Hospital and Medical Facilities, Public Health Service, U.S. Department of Health, Education and Welfare, Washington, D.C. 20201.

CURSOS POST-GRADUADOS

Feb. 7-10 CURRENT CONCEPTS OF INFECTIOUS DISEASE, Jefferson Medical College, Philadelphia, Pa.; Robert I. Wise, M.D., F.A.C.P., Director; Joseph F. Rodgers, M.D., Co-Director.

Feb. 14-18 MEDICAL GENETICS, The Johns Hopkins Hospital, Baltimore, Md.; Victor A. McKusick, MD., F.A.C.P., Director

Feb. 21-25 CANCER, Presbyterian-St. Luke's Hospital, Chicago, III.; Samuel G. Taylor, III, M.D., F.A.C.P., Director.

Mar. 7-11 THE BIG HEART, Cardiac Work and Cardiac Hypertrophy: Clinical Appraisals, Therapeutic Considerations and Pathologic Correlations, Baylor University College of Medicine, Houston, Texas; Raymond D. Pruitt, M.D. F.A.C.P., Director.

March 21 to April 2, 1966. The Department of Otolaryngology of the Illinois Eye and Ear Infirmary and the College of Medicine of the University of Illinois at Medical Center, Chicago, will conducts a postgraduate course in Laryngology and Bronchoesophagology. This course is limited to fifteen physicians and will be under the direction of Paul H. Holinger, M.D. It will be held largely at the new Illinois Eye and Ear Infirmary, 1855 West Taylor Street, Chicago, and will include visits to a number of Chicago hospitals. Instruction will be provided by means of animal demonstrations and practice in bronchoscopy and esophagoscopy, diagnostic and surgical clinics, as well as didactic lectures.

Interested registrants will please write directly to the Department of Otolaryngology, College of Medicine of the University of Illinois at the Medical Center, Postoffice Box 6998, Chicago, Illinois 60680.

Mar. 28 - April 1. BASIC MECHANISMS IN INTERNAL MEDICINE, University of Toronto, Toronto, Ontario, Canada; K. J. R. Wighaman, M.D., F.A.C.P., Director.

April 14-16. CURRENT CONCEPTS OF RENAL, GASTROINTESTINAL AND CIRCULATION PHYSIOLOGY, co-sponsored by the American Physiological Society, Barbizon-Plaza Hotel, New York, N.Y.; Daniel H. Simmons, M.D., F.A.C.P., and Charles Kleeman, M.D., F.A.C.P., Co-Directors.

April 25-28. The 1966 American Industrial Health Conference, will be held in Detroit, Michigan, with headquarters at the Sheraton Cadillac Hotel and meetings in Cobo Hall, it has been announced by the INDUSTRIAL MEDICAL ASSOCIATION and the AMERICAN ASSOCIATION OF INDUSTRIAL NURSES. This medical-nursing Conference which is comprised of the annual meetings of the two sponsoring Associations, will bring together approximately 2,000 persons which, in addition to industrial physicians and nurses. will include industrial hygienists, safety engineers, public health officials, military service medical personnel, university faculty members, management representatives and others who have an interests in the health of the working population. The annual meeting of the Industrial Medical Association will mark the organization's 50th anniversary meeting.

The scientific program, in which many of the nation's experts in the field of occupational health will participate, will be augmented by both scientific and technical exhibits. Intensive courses in selected areas of medical practice also will be presented. Further information about the Conference may be obtained by writing American Industrial Health Conference, 55 East Washington Street, Chicago, Illinois 60602.

May 9-13. INTERNAL MEDICINE IN LIGHT OF RECENT DEVELOPMENTS, Pennsylvania Hospital, Philadelphia, Pa.; Garfield G. Duncan, M.D., F.A.C.P., and Robert J. Gill, M.D., F.A.C.P., Co-Directors.

May 16-20. PHYSIOLOGICAL ASPECTS OF CARDIOPULMONARY DISEASE, Indiana Univ., Indianapolis, Ind.; John B. Hickam, M.D., F.A.C.P., Director.

May 23-25. NATIONAL TUBERCULOSIS ASSOCIATION. The 1966 Annual Meeting of the American Thoracic Association will be held in San Francisco, California.

June 13-17. ADVANCED PSYCHIATRY FOR INTERNISTS, Baltimore Psychoanalytic Institute, Baltimore, Md.; Ephraim T. Lisansky, M.D., F.A.C.P., Director.

June 15-18. NEUROLOGY FOR THE INTERNIST, Bowman Gray School of Medicine, Winston-Salem, N.C.; James F. Toole, M.D., F.A.C.P., Director.

Internacionales

CURSO COMPLETO DE GASTROENTEROLOGIA PARA GRADUADOS

A partir del 4 de marzo de 1966, se encontrará abierta la inscripción en el Departamento de Graduados de la Facultad de Ciencias Médicas de la Universidad Nacional de Buenos Aires, Paraguay 2155, para el Curso Completo de Gastroenterología que dictará en el Hospital Nacional de Gastroenterología "Dr. BONORINO UDAONDO", el Docente autorizado de Cirugía, Dr. Marcos Maur, con la colaboración de los siguientes Especialistas del mencionado Establecimiento: Dres. Manuel M. Ramos Mejía, Adolfo M. Rey, Victorino D' Alotto, Manuel Lemos García, Adolfo Schapira, Alfonso Fraise, Salomón Krigpún. Julio C. Rojas, Pedro Scorza, Leonardo Braier, Jorge Caffarello, Horacio Capizzano, Aldo Copello, Erman Crosetti, Emilio Chattás, Fernando Galindo, Atilio Iorio, Ricárdo A. Sabagh, Isaías Schor, Ramón Pando, Raúl Rodríguez, Alberto Apud, Ricardo de Elizalde, León Kesner, Antonio Musi, Gustavo A. Schickendantz, Ricardo Vivone y Luciano Bombaci. Actuará de Encargado Suplente del Curso el Docente autorizado de Cirugía Dr. Pedro Cotella.

El Curso tendrá una duración de 8 meses, desde el 4 de abril al 5 de diciembre. Los médicos inscriptos deberán concurrir todos los días hábiles de 7:30 a 12 horas, pudiendo inscribirse egresados de hasta cinco años. Para médicos residentes en otros países, no hay límite de antigüedad pero deben traer en el momento de inscripción, el título de médico o bien copia autenticada del mismo.

Está Previsto el Siguiente Programa Teórico:

Clases Magistrales los días lunes y Viernes a las 11 horas, sobre distintos aspectos de Fisiopatología Gastroenterológica abarcando toda la Patología Digestiva. Aprendizaje de los distintos medios complementarios de diagnóstico: Radiología, Endoscopía, Laboratorio, Clases de Dietología vinculadas a Patología Digestiva, Clases de Medicina Psicosomática en relación con la Gastroenterología.

Ateneos de: Radiología, Anatomía Patológica, Clínico-Quirúrgico y Bibliográfico así como un cursillo de Cirugía Experimental. Para las Clases Prácticas, que también tendrán desarrollo todos los días de 7:30 a 11 horas, se constituirán seis comisiones que rotarán por los siguientes Servicios; Clínica, Nutrición, Laboratorio de Investigaciones, Radiología, Endoscopía, y Proctología.

Los inscritos cirujanos, además de realizar instrucción en los Servicios indicados en el párrafo precedente, realizarán ejercicios de Cirugía Experimental y los tres últimos meses se adscribirán al Servicio de Cirugía del Establecimiento, donde actuarán en el mismo plano que los médicos becarios con que cuenta el Hospital.

El Departamento de Graduados de la Facultad otorgará certificación a los inscritos que hayan cumplido con el 80% de las actividades previstas. Para información complementaria dirigir carta al Director del Curso, Avenida Caseros 2061, Buenos Aires, Argentina, o bien personalmente a la Biblioteca del Hospital, tercer piso, teléfono No. 27-4641.

Feb 7-17 XI Curso Internacional de Angiología.

PROGRAMA

1º— Conceptos generales fundamentales para la comprensión de los trastornos circulatorios.

2º— La exploración del enfermo arterial. El interrogatorio. La exploración clínica. La angiografía. Errores de interpretación de los angiogramas.

3º— La arteriosclerosis. Su tratamiento médico. La cirugía de la arteriosclerosis. Operaciones simpáticas y reconstructivas. Sus indicaciones. Los riesgos de las prótesis artificiales.

4c— La tromboangeítis y otras arteritis inflamatorias no específicas. Tratamiento. La cirugía de la tromboangeítis. La simpatectomía, la neurectomía del tibial posterior y la suprarrenalectomía.

5º— La embolia artetrial. Las localizaciones de tratamiento médico y las localizaciones de tratamiento quirúrgico. La embolectomía simple. La embolectomía con trombosis. La embolectomía con arteriospasmo. Diagnóstico diferencial con otras oclusiones arteriales agudas.

6º— Comunicaciones arteriovenosas: Congénitas, traumáticas y espontáneas. Su repercusión local, regional y general. La fístula arteriovenosa terapéutica.

7º— El Síndrome de oclusión de los troncos supraaórticos (Síndrome de Martorell-Fabré). Formas completas e incompletas. La forma arterítica (Enfermedad de Takayasu) y la forma arteriosclerótica.

8º— La hipertensión arterial. Hipertensiones arteriales de tratamiento médico. Hipertensiones arteriales de tratamiento quirúrgico.

9º— La hipertensión portal. Tratamiento médico y tratamiento quirúrgico.

10º— La circulación venosa en los miembros inferiores. Exploración del enfermo venoso. Interpretación de flebogramas.

11º— Várices: Esenciales, postflebíticas, por aplasia del sistema venoso profundo, por comunicación arteriovenosa congénita. La varicografía. El soplo por reflujo. El fonovaricograma.

12º— Angiodisplasias congénitas (Malformaciones vasculares). l Síndrome de Klippel-Trenaunay. El Síndrome de Mafucci. Hemangiomatosis osteolítica.

13º— Trombosis venosas. Enfermedad tromboembólica. Clínica según su localización, evolución y etiología. Los anticoagulantes. La cirugía de la trombosis venosa. El Síndrome de Lian-Siguier-Welti.

14º— Secuelas postrombóticas. Insuficiencia venosa crónica.

15º— Ulceras de las piernas: Venosas, arteriales (Ulcera de Martorell), neurotróficas.

16º— Edèmas crónicos de los miembros: Flebedema, linfedema, quiledema, fibredema, mixedema y lipedema.

El 12 de febrero los Cursillistas y sus familiares que lo deseen podrán asistir a un "cocktail" en la residencia del Prof. Martorell y el día 13 a una excursión a Sitges con comida en un restaurante típico.
El coste de Inscripción es de 3,000 pesetas.
Día 17, Cena de Despedida.

OTROS

Agosto 20-25, 1966 Noveno Congreso Internacional de Enfermedades del Tórax.

Oct. 23-29, 1966 IX International Cancer Congress, Tokyo, Japan. A charter flight and several group flights are comtemplated, thus substantially reducing the cost of transportation. Members of the immediate family of congress participants will be eligible. Anyone interested should communicate with Hirsch Marks, M.D., 435 East 57th Street, New York 22, N.Y.

Instrucciones para los Autores:

El Boletín acepta para su publicación artículos relativos a medicina y cirugía y las ciencias afines. Igualmente acepta artículos especiales y correspondencia que pudiera ser de interés general para la profesión médica.

El artículo, si se aceptara, será con la condición de que se publicará únicamente en esta revista.

Para facilitar la labor de revisión de la Junta Editora y del impresor, se requiere de los autores que sigan las siguientes instrucciones:

a) Los trabajos deberán estar escritos a máquina a doble espacio y por un solo lado de cada página, en duplicado y con amplio margen.

b) En página separada debe incluirse lo siguiente: título (no excediendo de 80 letras y espacios), nombre del autor (es), institución y dirección postal del autor.

c) Artículos referentes a resultados de estudios clínicos o investigaciones de laboratorio deben organizarse bajo los siguientes encabezamientos: (1) introducción, (2) material y métodos, (3) resultados, (4) discusión, (5) resumen (en español e inglés), y (6) referencias.

d) Artículos referentes a estudios de casos aislados deben organizarse en la siguiente forma: (1) introducción, (2) observaciones del caso, (3) discusión, (4) resumen (en español e inglés), (5) referencias.

e) Las tablas, notas al calce y leyendas deben aparecer en hojas separadas.

f) Si un artículo ha sido leído en alguna reunión o congreso, así debe hacerse constar como una nota al calce.

g) Deben usarse los nombres genéricos de los medicamentos. Podrán usarse también los nombres comerciales, entre paréntesis, si así se desea.

h) Se usará con preferencia el sistema métrico de pesos y medidas.

i) Las fotografías y microfotografías se someterán como copias en papel de lustre sin montar. Los dibujos y gráficas deben prepararse a tinta negra y en papel blanco. Todas las ilustraciones deben estar numeradas (números arábigos) e indicar la parte superior de las mismas. Debe escribirse una leyenda para cada ilustración.

j) Las referencias deben ser numeradas sucesivamente de acuerdo con su aparición en el texto. Los siguientes ejemplos pueden servir de modelo:

6. *Koppisch, E.* Pathology of arteriosclerosis. Bol. Asoc. Med. P. Rico 46: 505, 1954. (artículo de revista).
4. *Wintrobe, M. M.* Clinical Hematology, 3rd Ed. Lea and Febiger, Philadelphia, 1952, p. 67. (libro).

Deben usarse solamente las abreviaturas indicadas en el Cumulative Index Medicus que publica la Asociación Médica Americana.

Instructions to Authors:

The Boletín will accept for publication contributions relating to the various areas of medicine surgery and allied medical sciences. Special articles and correspondence on subjects of general interest to physicians will also be accepted. All material is accepted with the understanding that it is to be published solely in this journal.

In order to facilitate review of the article by the Editorial Board and the work of the printer, the authors must conform with the following instructions:

a) The entire manuscript, including legends and references, should be typewritten double-spaced in duplicate with ample margins.

b) A separate title page should include the following: title (not to exceed 80 characters and spaces), author's name (s); institution, and author's mailing address.

c) Articles reporting the results of clinical studies or laboratory investigation should be

organized under the following headings: (1) introduction, (2) material and methods, (3) results, (4) discussion, (5) summary in English and Spanish, (6) references.

d) Case reports will include (1) introduction, (2) description of the case, (3) discussion, (4) summary in English and Spanish, (5) references.

e) Tables, footnotes and legends to figures should appear in separate sheets.

f) If the paper has been presented at a meeting, the place and date should be stated as a footnote.

g) Generic names of drugs should be used. Trade names may also be given in parenthesis, if desired.

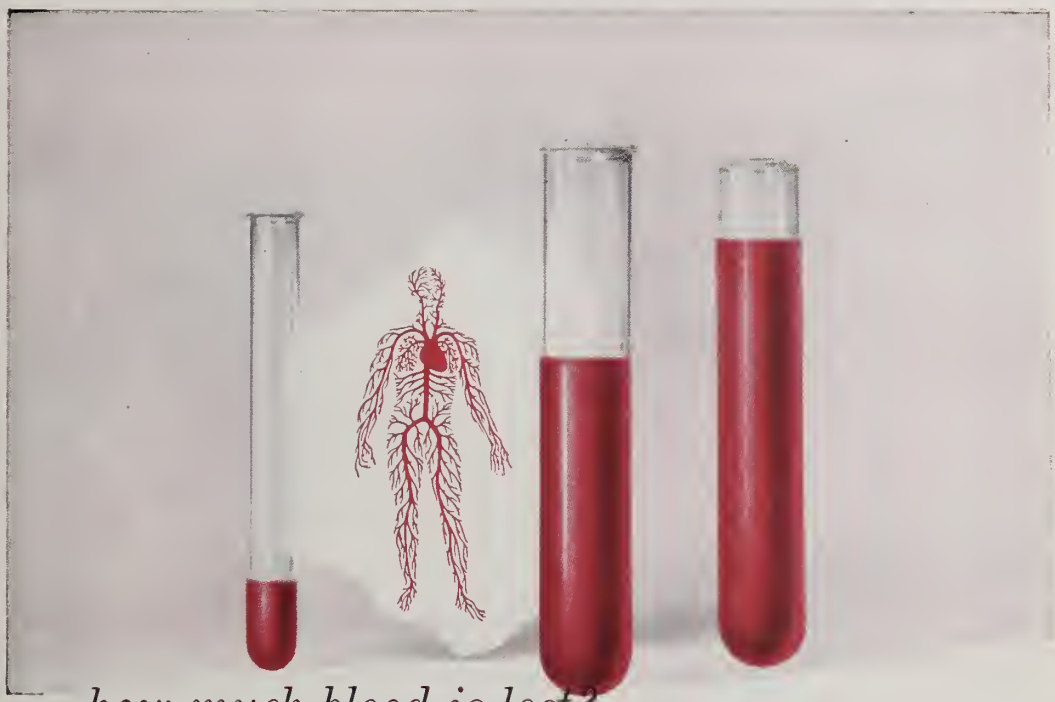
h) Metric units of measurement should be used preferentially.

i) Photographs and photomicrographs should be submitted as glossy prints, unmounted. Drawings and graphs should be made in black ink on white paper. All illustrations should be numbered (Arabic) and the top indicated. A legend should be given for each.

j) References should be numbered serially as they appear in the text. The following form will be used:

6. *Koppisch, E.* Pathology of arteriosclerosis. Bol. Asoc. Med. P. Rico 46: 505, 1954. (for journal articles).
4. *Wintrobe, M. M.* Clinical Hematology, 3rd Ed. Lea and Febiger, Philadelphia, 1952, p. 67, (for books).

Abreviations will conform to those used in the Cumulative Index Medicus, published by the American Medical Association.



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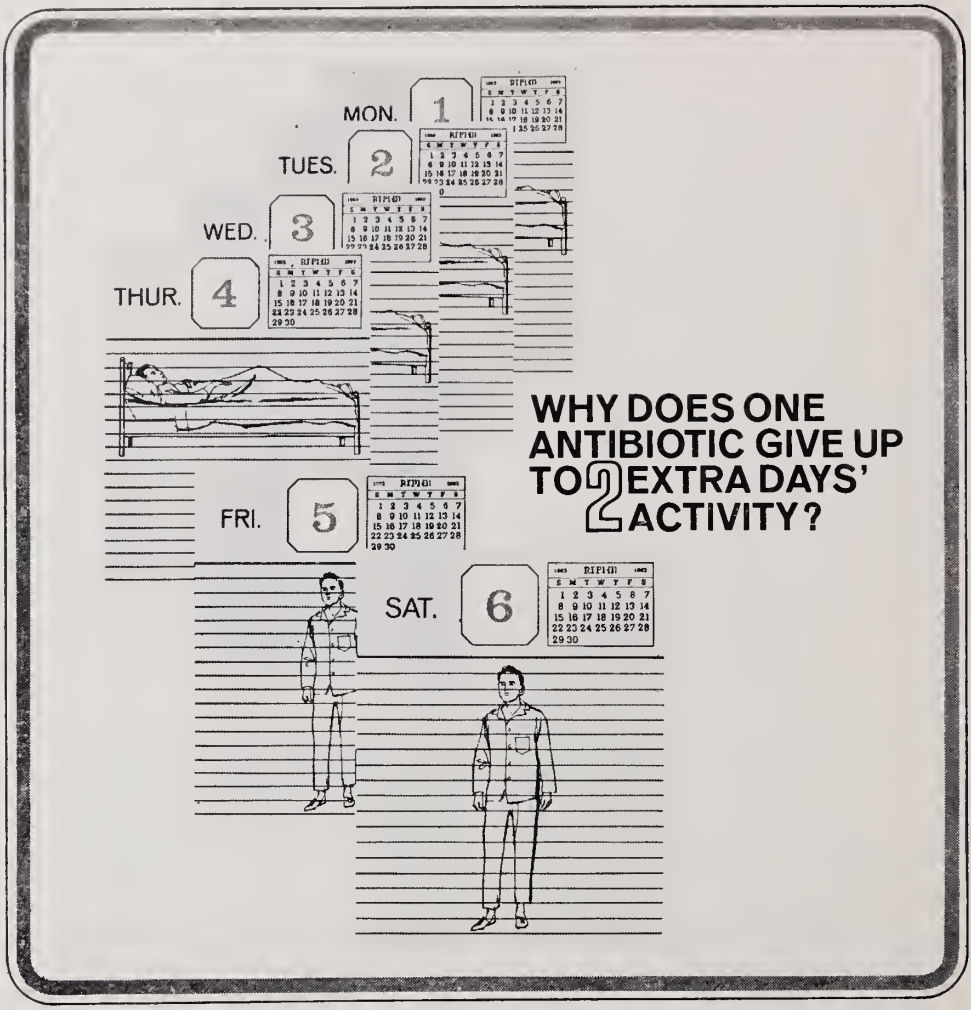
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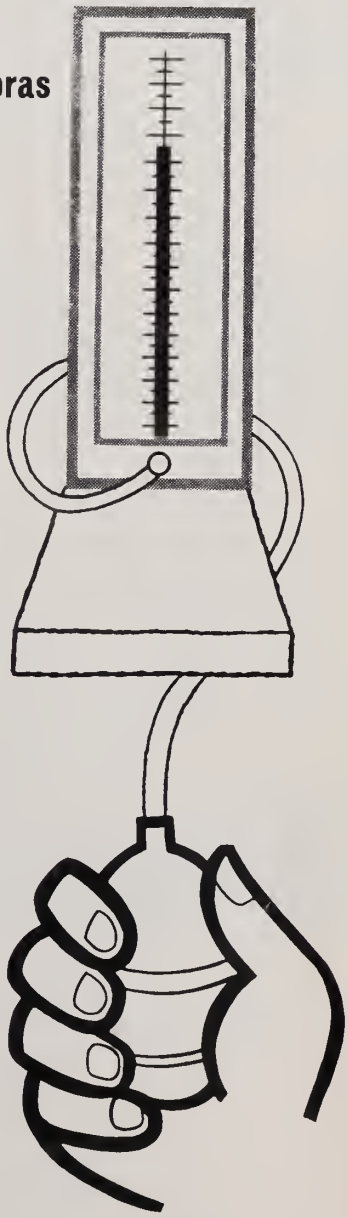
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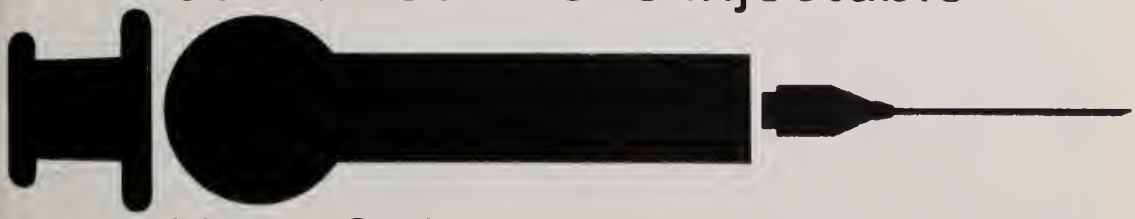
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ALLERGY TO COCKROACHES

Angel M. Marchand, M. D.

The pioneer work of Bernton and Brown (1) presented at the Twentieth Annual Meeting of the American Academy of Allergy, brought to the forefront a question which for years had haunted many inquiring minds, especially in the tropics, namely what part, if any, cockroaches played as etiologic agents in allergic illnesses.

Of the 55 species of the family, Blattidae Orthoptera in continental United States, Bernton and Brown consider seven or eight as a menace to indoor sanitation, and therefore as potential excitants of allergic disease. They limited their preliminary study to two species: The American cockroach *(Periplaneta americana)* and the Oriental cockroach *(Blatta orientalis)*. They prepared extracts of these two species, which were laboratory bred and they described their technique. (1)

In their survey to determine the incidence of skin sensitivity to cockroach extracts, Bernton and Brown (1) tested 253 normal individuals selected from the lowest social and economic strata of their population, and found an over all positive reactivity of 7.5% to at least one of the cockroach extracts. A second group of 114 allergic individuals was tested, and the percentage of positive skin reactions in this group was 28%.

They also performed passive transfer studies. In 22 of the 23 positive reactors studied, specific skin sensitizing antibodies were demonstrated.

They furthermore showed that their cockroach extract was heat stable, at least as far as the skin-testing properties of the extract was concerned. If the inmunizing properties prove to be likewise stable, much easier methods of preparation of extracts can be developed, as sterilization by heat would preclude the danger of contamination with the viral infections of which the roach has been a suspected vector.

Even though the work of Bernton and Brown (1) dealt exclusively with testing, they made this prophetic statements: "Our work with cockroaches paves the way to determine the allergenic potentials of other insects associated with food infestation. The present era is, indeed, a counterpart of that of mold allergy of 35 years ago." They conclude: "Desensitization with cockroach extract may reduce the number of refractory allergic patients, especially of those living in an insect-infected environment. This is the challenge."

When in 1939 I began to study allergic diseases in the tropics, I was impressed when examining microscopically my pollen and mold slides, exposed to the outside air, with the frequent appearance of small pieces of legs and wings of cockroaches, apparently air borne. For many years I had suspected that the so called "intractable asthma," in many instances was possibly the result of an allergy to cockroaches. In many of them I found a

Presented in part at the 63rd. Annual Meeting of Puerto Rico Medical Association, November 10, 1964, San Juan, P. R.

positive reaction to an extract of silk for no apparent reason, save for the possibility of a cross-reaction with cockroaches or other insects. Treatment with silk extracts, however, proved to be repeatedly ineffectual.

If you live in the tropics, it is impossible to avoid contact with roaches. Roaches die, disintegrate, and form part of our house dust. They infest with their bodies and with their secretions many foods especially chocolate and wheat. This is a factor of paramount importance when one considers the heat stable properties of the roach.

I was unable to produce a suitable roach extract that would give any positive reactions in these sensitivity tests, possibly because I used only the wings and legs. However, an extract prepared from the whole body of the insects, as described by Bernton and Brown, proved adequate. Its use suggested a possible paralellism of our experience with allergy to bats.

Allergic reactions to bats are very common in Puerto Rico and in many of our asthmatics, allergy to bats is of paramount importance. Desensitization is frequently necessary to control the attacks. It is interesting, however, to note that in my experience many of these patients show no reaction to extracts of bat-skin or bat-hair, but show a definite reaction to bat droppings. Sensitivity to the latter is quite common, and in my experience to date, bears no relation to mold allergy, nor even to common house dust sensitivity. The extracts of bat droppings are so highly allergenic that extreme care must be observed both in testing and treatment, as constitutional reactions are frequent. When this sensitivity, however, is observed the results from desensitization are not only most satisfactory, but also frequently dramatic in the speed of favorable response.

With this experience as background, we contacted Dr. Harry S. Bernton and proposed to do a survey of our allergic population, using the same extracts which he and Dr. Brown had used in Washington.

The use of Oriental and American roach extracts was a happy coincidence, because our most common roach is the *Periplaneta* (American roach). We do not have the Oriental roach. The use of these two extracts, therefore, gave us an extra factor for comparison. In Table I, a list of the most common roaches in Puerto Rico is presented.

TABLE I: COMMON COCKROACHES IN PUERTO RICO

Common name	*Scientific name*
American	*Periplaneta americana*
	" *australiana*
	" *brunea*
German	*Blatella germanica*
Brown - banded	*Supela supellectillum*
Fatula	*Leucophea maderae*

Materials and Methods

We decided to test the Oriental and American roach extracts, comparing them to a commercial silk extract, for reasons previously stated. All tests were done intracutaneously with a 1-1,000, 1-100 and if negative a 1-10 dilution of the roach extracts (46,000 P.N.U. per ml. for *Blattela* and 74,000 P.N.U. per cc. for other roach extracts). The silk extract was Hollister-Stier's and a concentration of 1-200 was used in testing.

Our patients were mostly of the middle to higher socio-economic level. Ages ranged from a low of 3 years to a high of 82 years. Their age distribution is shown in Table IV. There were no sex differences in the number of patients or reactors. All patients came to my office or were referred for a supposedly allergic illness. However, of a total of 284 patients, 170 (60%) suffered from bronchial asthma. The remainder were cases of

allergic rhinitis, with but few cases of dermatitis, urticaria or headaches.

After the first 177 patients had been tested, Drs. Bernton and Brown supplied us with an extract of German roach *(Blatella germanica)*, a roach that is also very prevalent in Puerto Rico. We incorporated this extract in the last 130 patients tested, including 23 previously tested.

TABLE IV: AGE DISTRIBUTION OF PATIENTS TESTED

Age	No.	Positive	Negative
Under 10	19	7	12
10-20	62	31	31
21-30	59	36	23
31-40	53	33	20
41-50	46	18	28
Over 50	45	21	24

Results

TABLE II: SKIN TESTS PERFORMED POSITIVE REACTORS

Patients Tested	Oriental Roach		American Roach		Silk		German Roach	
	No.	%	No.	%	No.	%	No.	%
284	52	18	126	48	50	18	—	—
130	23	18	56	43	21	16	34	26

Table II shows the results of tests done from Jan. 4, 1965, through October 30, 1965. Of the total of 284 tested, 48% were positive to the American Roach. Only 18% were positive to the Oriental roach, which we do not have, but over 60% of these positive reactors had visited continental U.S. where sensitivity could have developed. The cross-reaction does not seem to be as great as found by Bernton and Brown. It is interesting that 50 patients (18%) showed a cross-reaction to silk.

Of the 130 patients tested with *Blatella germanica* there were 34 (26%) positive reactors. All indications are to the effect that our worst offender as an etiologic agent is the *Periplaneta.*

Table III shows that of a total of 170 asthmatics in the group, a positive reaction to one or more roach extracts was found in 88 (52%). The high incidence is of course explained in part by the fact that these

TABLE III: ASTHMATIC PATIENTS

Number	Positive Reactors to One or More Roach Extracts	
	No.	%
170	88	52

patients are really a selected group, as they seek my help after failure to find relief elsewhere.

As soon as the large number of positive reactors began to appear, we felt it necessary to consider desensitization therapy, especially in the asthmatics. To eliminate as much as possible the effect of the psychic influence in the results, no patient was advised of the nature of the extract used for testing or for treatment. Whenever an explanation was insisted upon, we usually referred to the extract as "special dust extracts." Depending on the skin reaction we ordinarily started treatment with 7.4 or 74 units, and worked up in biweekly or weekly injections to a top dose of 1,000 to 1,500 P.N. units.

When other factors such as infection or concomitant allergies were eliminated, the results of specific desensitization with cockroach extracts were very frequently dramatic, the patient feeling well after the third to the fifth injection.

Discussion

Only time and experience will tell us, among other things, how long treatment with this extract is necessary to maintain a patient free of this sensitivity.

We have purposely avoided the use of water-in-oil emulsions in treatment with roach extracts fearing possible formation of an abscess. There is, however, no inmunologic ground for this fear, because there seems to be no delayed reactions at all from the extracts. The whole mechanism seems to be on the basis of a highly specific reaginic response.

At present we have under this specific desensitization 125 patients including most of the asthmatics who have proved to be definite positive reactors.

In general the results are most encouraging and we hope to be able to present a clinical evaluation of them in the near future.

The favourable results in asthmatics are usually dramatic. There are other instructive observations worth mentioning.

One patient with vascular headache of the migraine type, of 8 years' duration is now free of these headaches after desensitization with *Periplaneta* extract. On 3 occasions her tolerance dose was exceeded and typical migraine was provoked. Whereas once she could not eat chocolate or wheat (a source of roach infestation), she now tolerates both with no ill effects. Also under treatment I have three cases of allergic dermatitis in which cockroach allergy definitely seems to play a very important etiologic role. The cases of allergic rhinitis apparently from roach sensitivity are numerous, and specific desensitization is frequently mandatory.

Summary

The role of cockroaches as etiologic agents in allergic illnesses is discussed.

The cutaneous response of 284 allergic individuals in Puerto Rico was studied, revealing 48% positive reactors to an extract of our most common roach, *Periplaneta americana.*

Among 130 allergic patients tested with an extract of the German Roach *(Blatella germanica)* there were 26% positive reactors.

Of the 170 asthmatics studied, 88 (52%) showed a positive reaction to one or more of the roach extracts. It seems that allergy to roaches plays an important etiologic role in at least some of the so called "intractable asthma" patients.

An 18% positive skin reaction to silk, and also 18% to Oriental Cockroach *(Blatella orientalis)* was found. The oriental roach is non-existent in Puerto Rico. The mechanism of cross-reaction may explain, in part, these positive reactions.

Desensitization with specific roach extract is being carried out, apparently for the first time. The results to date are most encouraging, frequently dramatic, and will be the subject of a subsequent report.

Resumen

Se presenta y discute el problema de las cucarachas como agentes etiológicos en las enfermedades alérgicas.

Se estudió la cuti-reacción de 284 pacientes alérgicos en Puerto Rico, demostrándose una reacción positiva en 48% de ellos a un extracto de *Periplaneta americana,* nuestra cucaracha más común.

Entre 130 pacientes alérgicos, la cutireacción positiva a la *Blatella germánica* (cucaracha alemana) fué de 26%.

Se estudiaron 170 asmáticos y 88 (52%) de ellos demostraron una cuti-reacción positiva a extractos de una o más cucarachas.

Aparentemente la alergia a cucarachas juega un papel etiológico importante en por lo menos algunos de los pacientes con "asma de origen desconocido".

Se encontró una cuti-reacción positiva de 18% a extractos de seda, y también de 18% a la cucaracha oriental *(Blatella orientalis)*, la cual no existe en Puerto Rico. El mecanismo de "reacción cruzada" probablemente explique en parte estos hallazgos.

Se ha ensayado la desensibilización con extractos específicos de cucarachas aparentemente por vez primera. Los resultados hasta la fecha son muy halagadores, a menudo dramáticos, y serán objeto de un informe subsiguiente.

Acknowledgment

The author is indebted to Dr. Harry S. Bernton and Dr. Halla Brown from Washington, D.C., who supplied the materials for this study, and without whose help and guidance the work would not have been possible. Our thanks also to Dr. Luis Felipe Martorell, Entomologist of the Experimental Station of the University of Puerto Rico, who instructed us in the identification of the roaches, and placed his collection at our disposal.

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SODIUM D-THYROXINE IN TROPICAL SPRUE

R. Rodríguez-Molina, M.D., D. Sc. (Med)., F.A.C.P.
Marta Cancio, Ph. D.

Tropical sprue is a term applied to a clinical syndrome that is characterized among other manifestations, by a state of malabsorption at the level of the small intestine (jejunum and ileum). The etiology of sprue is unknown. It is believed that biliary and pancreatic secretions and enzymes are not appreciably affected. Dietary fats, proteins, carbohydrates, electrolytes, and water are poorly absorbed. Anatomical changes in the mucosa of the ileum and jejunum are associated with abnormal tests for intestinal absorption, such as D-xylose excretion and vitamin A absorption. Fat balance studies are employed to determine the presence and severity of steatorrhea. Daily determination of the amount of fat in the stools is considered a highly reliable means for detecting intestinal malabsorption, as day to day variations of fat content in the stools frequently occur. This procedure, however, is a laborious process requiring close surveillance of patients by personnel in charge. A dietitian is needed to prepare and serve the diets and to see that patients eat as much as possible, day by day. A laboratory technician is required to determine the fat contents of diet and feces by chemical analysis.

From the General Medical Research Laboratory and the Medical Service, Veterans Administration Hospital, San Juan, Puerto Rico.

Investigation carried out with funds granted by Baxter Laboratories, Inc., Morton Grove, Illinois, U.S.A.

The majority of the clinical symptoms of tropical sprue are believed to be reflections of nutritional deficiencies, which result from impaired absorption associated with abnormal intestinal activity.

It was proposed to observe in this study possible beneficial effects that dextrothyroxine might have on absorption of nutrients, particularly fats and carbohydrates as indicated by the tests mentioned above.

Materials and Methods

Documented sprue patients (males) who met the criteria for the condition as set forth by Rodríguez-Molina and others in 1960 (1), were studied. Diagnostic criteria included the following: insidious onset, chronic symptoms and infrequent spontaneous remission, gastrointestinal disturbances (dyspepsia*, diarrhea, and steatorrhea), stomatoglossitis, with or without atrophy of the lingual papillae, early weight loss accompanied by increasing weakness and prostration, free hydrochloric acid in the gastric secretions (in over 90% of the cases), macrocytic, hyperchromic anemia associated with a megaloblastic marrow and absence of neurologic manifestations in about 90% of the cases. Other laboratory findings are impaired vitamin A absorption, low d-xylose excretion and a daily fat level in the stools of over 6 grams.

In order to determine the presence and degree of steatorrhea in a sprue patient it is necessary to administer a standard test diet (STD) containing

**This term comprises, in order of frequency, abdominal distention, epigastric distress (not necessarily related to the taking of food), heartburn, and generalized abdominal discomfort and pain.*

a constant amount ot digestible fat in addition to other foodstuffs and to determine the total daily output of fat in the feces. The STD consists of fruit juices, dry breakfast cereals, cream of wheat, white bread, potatoes, three different salads of lettuce with fruits and dressings, cooked rice, jelly, baked apple, water-packed fruits, string beans, carrots, one or two eggs, lean beef or lamb, butter and one liter of milk per day. Three menus are made up from the food items which, if fully consumed, supply between 90 to 100 grams of fat and about 10 grams of gluten per day.

The STD was given for a preliminary period of study lasting 8 days. Starting on the third day, collection of 24 hour stools was begun. In our experience the period of 8 days is enough to demonstrate presence of steatorrhea. On the ninth day of study D-thyroxine was started in 2 mg daily dose.

Trials with D-thyroxine comprised four different periods: (1) Preliminary period lasting 8 days, (2) period when 2 mg daily of drug was given to each patient (8 days), (3) period when 4 mg daily of drug was administered (8 days), and (4) a variable period of 8 to 15 days of additional observations following completion of drug administration. The steatorrhea test diet was given throughout all periods, and daily fat balance studies were carried out throughout the entire study. D-xylose excretion (using 5 g of the sugar) and vitamin A absorption tests were performed weekly on each patient.

The amount of fat in the diet and in the stools was determined daily by chemical analysis, in terms of total fatty acids, by the ether extraction method described by Van de Kamer (3). Other tests for intestinal absorption were performed in accordance with standard accepted procedures. Peripheral blood studies such as red blood cell counts, hemoglobin determinations and hematocrit were also performed.

Results

Twelve patients, aged 60 to 72, were studied.

Three cases showed a decrease in steatorrhea during or following administration of the drug (See Table I). Some improvement in other intestinal absorption tests was noted. Mild clinical improvement was observed. As steatorrhea subsided diarrhea improved, associated with some gain in weight (3-5 pounds), and slight improvement in the appearance of the tongue. However, peripheral blood values (red blood cells, hemoglobin, hematocrit) did not improve. Five patients showed no improvement in their clinical picture, no change in steatorrhea and other tests for intestinal absorption, and no alteration of peripheral blood values. These eight patients were in a state of chronic relapse of the disease.

The other four were in clinical remission. Results of fat balance determinations and other tests for intestinal absorption were found within normal limits. These cases were employed to find out whether dextrothyroxine in the same doses given to the other eight patients might produce steatorrhea. The drug did not produce steatorrhea in these patients.

No toxic reactions to D-thyroxine were observed.

Discussion

As shown in Table I, the first three patients studied presented evidence of improved intestinal absorption during and following administration of D-thyroxine. Improvement in clinical picture was associated with the improved absorption although peripheral blood values remained unchanged. These gratifying results prompted the authors to continue the study. However, the following five consecutive cases failed to show improvement. It was suggested that administration of daily amount of drug (4 mg) be extended from 8 to 30 days. After due consideration, this suggestion was not ac-

TABLE I: EFFECT OF D-THYROXINE ON FECAL FAT EXCRETION IN TROPICAL SPRUE. *

Patient Nº	Preliminary (8 days) 1	D-Thyroxine 2 mg/day (8 days) 2	D-Thyroxine 4 mg/day (8 days) 3	Post-therapy (8-15 days) 4
1	16.1 ± 11.5	17.1 ± 8.8	5.9 ± 3.6	1.8 ± 2.1
2	7.8 ± 6.2	6.4 ± 4.1	2.4 ± 2.0	0.86 ± 0.47
3	24.6 ± 12.7	8.4 ± 5.4	6.7 ± 2.7	—
4	6.8 ± 4.4	13.0 ± 5.2	13.1 ± 4.9	12.2 ± 9.9
5	9.7 ± 2.8	11.8 ± 3.5	10.6 ± 2.9	7.4 ± 4.5
6	17.3 ± 4.9	18.7 ± 3.9	22.0 ± 3.3	19.0 ± 10.7
7	15.0 ± 7.2	16.6 ± 3.2	16.0 ± 2.1	10.0 ± 4.6
8	6.1 ± 3.3	4.1 ± 7.2	4.1 ± 2.6	6.0 ± 1.7
9	1.5 ± 0.81	1.5 ± 1.1	0.49 ± 0.41	—
10	0.45 ± 0.44	0.68 ± 0.42	0.75 ± 0.46	0.83 ± 0.73
11	0.44 ± 0.21	2.15 ± 2.2	1.99 ± 0.89	0.99 ± 0.49
12	2.66 ± 2.2	2.92 ± 2.7	6.70 ± 3.2	7.90 ± 11.6

** All figures in this table represent total daily fecal fat excretion expressed in grams, mean ± 1 S.D.*

cepted because it was felt that condition of patients might become aggravated. In accordance with results obtained in previous studies, it was believed that 15 days under a given treatment was enough to bring about some changes in the malabsorption and in the clinical picture.

Sodium D-thyroxine stimulates the liver to increase oxidative catabolism and excretion of cholesterol and its degradation products via the biliary route into the feces. Hence, the action of sodium dextrothyroxine must be physiological, inasmuch as it constitutes a stimulus to a normal excretory mechanism (2). Whether this mechanism of action was instrumental in improving intestinal absorption in the first three cases reported, is not known. On the other hand, results may have been due to the element of chance, as it is not infrequently happens in clinical trials involving a small number of patients.

Summary

A study comprising 12 sprue patients (8 in chronic relapse, 4 in remission), was carried out with the purpose of observing the effect of sodium D-thyroxine (Choloxin-Baxter) in tropical sprue.

The therapeutic action of the drug on clinical aspects, steatorrhea, D-xylose urinary excretion and vitamin A absorption was noted.

Doses of D-thyroxine administered to each patient: 2 mg daily over 8 days, followed by 4 mg daily over 8 more days, for a total of 48 mg per patient.

The first three cases studied exhibited improvement of intestinal absorption, as ev-

idenced by a decrease in steatorrhea, an improvement in other tests for intestinal absorption. Some clinical improvement was observed.

No improvement was noted in five other patients.

Four patients in a state of remission were also studied. Under the conditions of the clinical trials, D-thyroxine did not produce any significant change nor did it appear to alter the normal fat content of the stools of these patents.

No toxic reactions to the drug were observed.

Resumen

Un estudio incluyendo 12 pacientes de esprú, 8 pacientes en estado crónico de la enfermedad y 4 en remisión, se llevó a cabo con el propósito de observar la acción de D-tiroxina sódica (Choloxin-Baxter) en el esprú tropical.

Se estudió la acción de la droga en los aspectos clínicos, en la esteatorrea, en la excreción urinaria de D-xylosa y en la absorción de vitamina A.

La dosis de D-tiroxina administrada a cada paciente: 2 mg diarios por 8 días, seguidos de 4 mg diarios por 8 días, adicionales, alcanzando un total de 48 mg por paciente.

En los primeros 3 casos estudiados se observó mejoría de la absorción intestinal demostrada por una disminución en la esteatorrea, y por mejoría de las otras pruebas de absorción intestinal. Se notó una ligera mejoría en la sintomatología clínica.

Por el contrario no se observó mejoría alguna en 5 pacientes estudiados posteriormente.

Cuatro pacientes en estado de remisión fueron incluídos en este estudio. Bajo las condiciones de este estudio, la D-diroxina no produjo esteatorrea, ni afectó en forma alguna el contenido de grasa en las excretas de estos pacientes.

No se notaron reacciones tóxicas a la droga en ninguno de los pacientes estudiados.

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PULMONARY ALVEOLAR PROTEINOSIS
Diagnosis and Treatment

José Ramírez Rivera, M.D.

Alveolar proteinosis is a pulmonary disease of world-wide distribution and recent vintage. It was first described in 1958 (1), on the basis of 28 biopsy and autopsy cases, and since that time an additional 80 cases have been added to the literature. Individuals in industrialized nations appear to be more susceptible to the disease. Most cases have been observed in the United States, but a few have been seen in Great Britain, France, Germany and Italy. Two cases have been reported from Japan and one from Oceania. There have been no reports from South America.

The cause of the disease is unknown and its clinical course has not been well delineated. Rapid progression, spontaneous remission, and long-standing pulmonary infiltrates have all been observed. Twenty-five per cent of the reported cases have died. While a few cases appeared to have died of asphyxia, many others have succumbed to pulmonary fungal infections. The large number of fatal infections caused by *Nocardia asteroides* (2) and members of the *Aspergillus* genus (3) can now be explained by the fact that the bronchoalveolar contents of patients with alveolar proteinosis provide the nutritional requirements for the luxuriant growth of *N. asteroides* and *A. fumigatus* (4).

The purpose of this paper is to review the pathogenetic concepts which have emmerged from the study of six men and three women with alveolar proteinosis, and to discuss diagnosis and treatment in terms of these concepts.

Pathogenetic Concepts

The hallmark of alveolar proteinosis is the accumulation of viscous and acellular material in the alveoli in the absence of an inflammatory response (Fig. 1). From the freshly cut surface of the lung, a viscous yellowish-white substance exudes which, on chemical analysis, can be shown to contain large amounts of lipid. Recent electron microscopic observations suggest that the lipid material originates, at least in part, as a secretion or breakdown product of the granular pneumonocyte, one of the cells lining the alveolus (5).

On long term observation of nine cases, two phases of the disorder became apparent: an accumulation phase and a clearing phase. In some cases, a relentless occupation of the pulmonary parenchyma occurred over a period of weeks or months; in others, partial clearance of the pulmonary infiltrates

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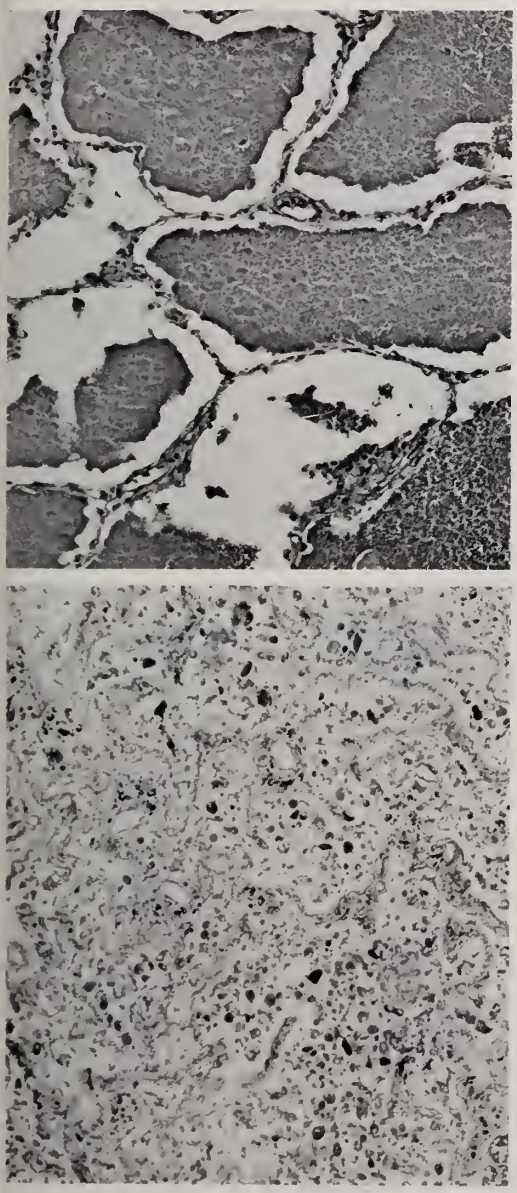


Fig. 1: Photomicrographs showing (A) Variously filled pulmonary alveoli in the absence of inflammatory response. (PAS stain, x 175) (B) mononuclear cell response observed in biopsy obtained one week after terminating endobronchial infusions. (PAS stain, x 140)

was observed. By giving radioiodinated albumin intravenously, pulmonary sequestration of plasma proteins was demonstrated during the accumulation phase in some patients (6). In addition, studies of the total tracheobronchial clearance of inhaled graphite particles demonstrated a marked slowing of the mucous blanket while there was widespread filling of alveoli by this viscous material, and an increase in the rate of motion of the mucous blanket during remission (6). This slowing of the mucous blanket is certainly one cause for the extensive inspissation of viscid bronchial secretions noted in this disease, and it probably contributes to the susceptibility of patients with alveolar proteinosis to repeated pulmonary infections. Biopsies were performed on four patients at one, two, three, and eight weeks after pulmonary irrigation. The striking increase in cellularity in the early specimens suggested that once the material was hydrolyzed, it was removed by a phagocytic response (Fig. 1B). Detailed respiratory function studies demonstrated that once the material was removed physiologic restitution was nearly complete (6,7,8,9). Although the cause of the disease remained unclear, its clinical and pathophysiological features were well explained in terms of a dysfunction of the pulmonary clearing process (7).

Diagnosis

The presenting complaints of the nine patients were quite varied. Some were first seen with an asymptomatic pulmonary infiltrate; others complained of breathlessness on exertion or a cough productive of scanty viscid sputum. In two cases, the sputum was occasionally blood-stained, and rarely contained yellowish-white fragments which, on

close scrutiny, were quite characteristic. Most patients sought medical attention because of persistent pulmonary infiltrates and repeated infection. Besides the lung, no other organ was involved, but the serum of one patient was persistently hyperlipemic (6). Physical findings were few. Rales were heard particularly over the lower half of the chest. Cyanosis and clubbing of the fingers were a feature of only the three more advanced cases; and cor pulmonale was seen only once, on a 30-year old man who had been cyanotic and bed-ridden for ten months (9).

The lesion began most commonly as a diffuse pulmonary process. It was usually bilateral and in the areas of greatest radiodensity — the midlung fields; but patchy infiltrates occurred in any lobe and infiltrates appeared in one lobe at a time when they were disappearing from another (Fig. 2). A host of roentgenographic patterns were created by patchy clearing or patchy development of these infiltrates, but changes in cardiac contour or pleural effusions were not observed. Unlike sarcoidosis, no hilar adenopathy was present.

Besides the roentgenogram, the level of the serum lactic acid dehydrogenase (LDH), when elevated, was useful in diagnosing the disease. The level of LDH appeared to be related to the activity of the disease rather than to the roentgenographic appearance. It was elevated in the absence of liver or cardiac disease in the active and progressive cases, but in two cases with long standing and extensive pulmonary infiltrates it was not increased. The triad of a persistently elevated level of LDH, chronic evolving acinar pulmonary infiltrates, and a patient whose pulmonary complaints were limited to breathlessness, has been observed only in alveolar proteinosis.

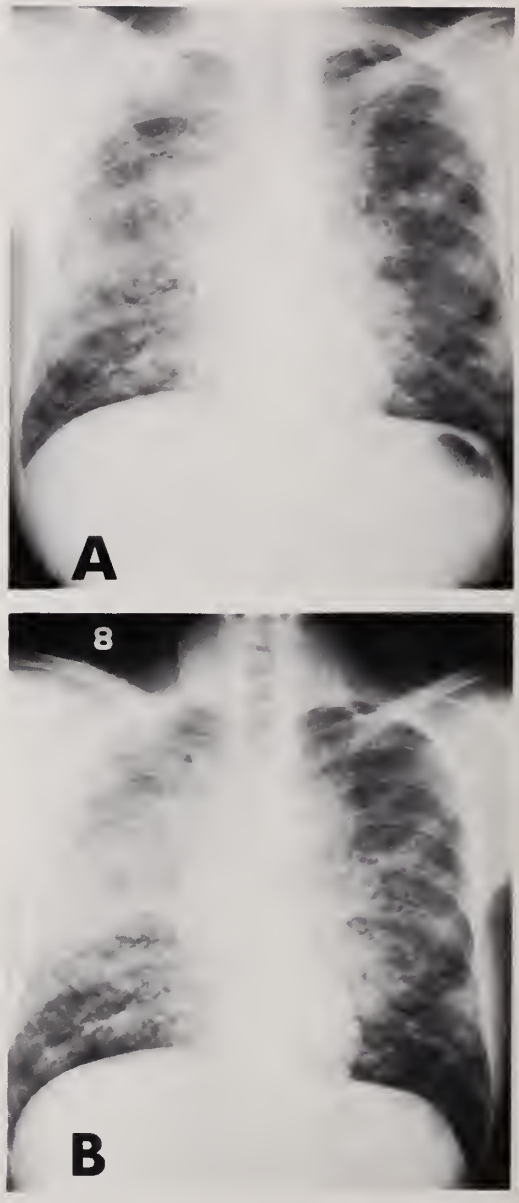


Fig. 2: Roentgenograms obtained one month apart in asymptomatic patient. "B" shows increased infiltration in right upper lobe while infiltrates at the apex and lower lobe of left lung have partially cleared.

Although alveolar proteinosis may be suspected from clinical and laboratory observations, the diagnosis can only be established with certainty by demonstrating the characteristic alveolar material in tissue sections or in histologic preparations of the sputum. We have recently demonstrated that the bronchial excretions of four patients treated by repeated irrigation of pulmonary segments contained diagnostic samples of alveolar material more than 50% of the time, and that when the whole lung was lavaged, large amounts of diagnostic material could always be obtained (10). The proteinaceous material was identified more easily when the sections of sputum were stained with Alcian green medium rather than with PAS, the stain classically used. While PAS stains both the mucous secretions and alveolar material similarly, Alcian green stains, the mucous green and the alveolar material yellow.

Treatment

Once the diagnosis was established, bronchopulmonary irrigation was performed in the patients with progressive disease with 0.9% saline solutions containing heparin, acetylcysteine, or a combination of both agents. Solutions containing 5.0 - 7.5 units of heparin per ml and 1% acetylcysteine were well tolerated even when used in large amounts.

The first six cases were treated successfully by repeated segmental irrigations through a semi-permanent endobronchial catheter introduced percutaneously through the cervical trachea (6,7,8). Irrigations were performed four times daily with 100 ml. of solution. Because this solution was not irritating, and was introduced beyond the trigger areas of cough, cough was only produced when the individual segments were

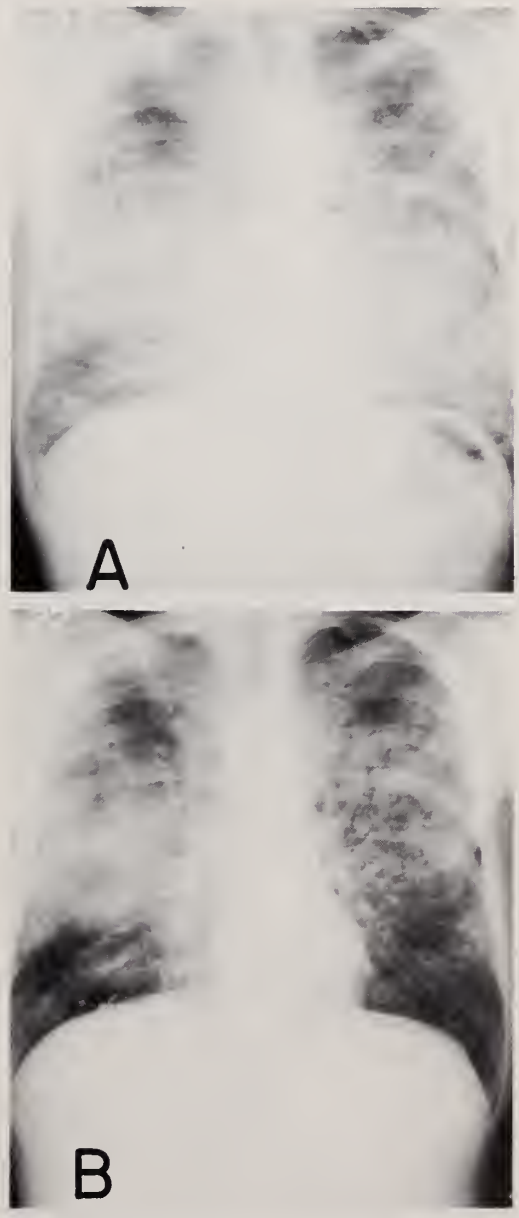


Fig. 3: Roentgenograms. (A) Before treatment, showing diffuse and massive granular infiltrates. (B) One month later, after repeated irrigations of the left lower lung, showing extensive clearing of treated segments.

filled to overflowing. In three of the patients, the pulmonary infiltrates began to clear after receiving only two weeks of treatment to each side (Fig. 3), but in the three others, months of treatment were required, and in two of the three, only partial improvement was obtained.

Although segmental pulmonary irrigation was simple and effective, it took many weeks of hospitalization and was poorly tolerated by hypoxic patients. For this reason, in the past year a method for lavaging one entire lung at a time was evolved (11). This method has been safe and efficient. It is based on separating the ventilation of each lung with a dual-channel bronchospirometry tube and filling one lung with fluid while the other lung is ventilaed with 100% oxygen (Fig. 4).

During the first twelve lavages, the mechanics of the lavage were provided by the patient — the fluid was inhaled and exhaled for ten minutes and evacuated. More recently, however, by using a tidal principle, the lung has been filled and evacuated without the cooperation of the patient, and with greater speed (9). Using this method, lungs have been washed with as much as 12.5 liters of irrigating solution in a 45-minute period, and large amounts of alveolar material have been removed.

The uniqueness of massive bronchopulmonary lavage was dramatized by a recent case transferred to Baltimore with severe pulmonary insufficiency, cor pulmonale, and secondary polycythemia. This 30-year-old man was hypoxic at rest even though receiving oxygen constantly — because more than 50% of the cardiac output was perfusing an unventilated capillary bed. Segmental pulmonary irrigation had been tried repeatedly elsewhere over a period of three months,



Fig. 4: Filling the right lung with fluid while ventilating the other lung with oxygen.

but it had failed because of inadequate ventilatory capacity to expel the viscous bronchoalveolar contents. Each lung was irrigated five times with a combined total of 39.7 liters of solution. Nearly six liters of proteinaceous material were removed. By the end of this period, the level of LDH which had been elevated for over 15 months had reached normal levels and he had achieved an almost complete clinical, roentgenographic and physiologic restitution (9).

Discussion

The first six cases of alveolar proteinosis

treated by pulmonary irrigation have been followed now for more than 16 months. Two of these cases have been followed for more than two years. Pulmonary infiltrates recurred in one patient 13 months after the lavage. The drop in lactic acid dehydrogenase following bronchopumonary lavage and the limited recurrence in these patients indicates that the retained alveolar contents may perpetuate the disease by injuring the alveolar lining cells. For these reasons, and because of the high prevalence of life-threatening infections, I believe that cases of alveolar proteinosis should be promptly treated if they have reached an indolent stage or if the disease appears to be progressive.

Summary

Alveolar proteinosis is a rare disease of recent vintage which manifests itself as a dysfuncton of the pulmonary clearing process. Based on this concept, diagnostic and therapeutic criteria have been evolved through long-term observations of nine cases. The disease may be suspected when mottled shadows appear in the roentgenogram indicating filling of the pulmonary air spaces. This suspicion may be given added weight when a persistent elevation of the serum lactic acid dehydrogenase is observed in association with patchy development and resolution of pulmonary infiltrates in patients with no evidence of systemic disease. The diagnosis can be definitely established by finding the characteristic alveolar material in histologic preparations of the sputum or of lung tissue. Bronchopulmonary irrigation through repeated segmental flooding and, preferably, whole lung lavage has been an effective treatment. Recent experience has shown that whole lung lavage may be effective even when segmental irrigation is not well tolerated or has failed.

Resumen

La proteinosis alveolar pulmonar es una enfermedad rara de orígen reciente que se manifiesta como una malfunción de los mecanismos que mantienen las vías respiratorias limpias y funcionales. Basado en este concepto, nuevos criterios sobre diagnóstico y tratamiento se han desarrollado durante el estudio de nueve casos. La enfermedad se puede sospechar cuando la radiografía muestra imágenes moteadas sugiriendo una acumulación de material en los alvéolos. A esta sospecha se le da más valor cuando se observa una elevación de la deshidrogenasa láctica del suero, asociada con clarificación y recrudecimiento de los infiltrados pulmonares en ausencia de manifestaciones sistémicas. El diagnóstico se puede establecer definitivamente encontrando el material alveolar característico en preparaciones histológicas del esputo o del tejido pulmonar obtenido por biopsia. La irrigación bronquiopulmonar usando una técnica de inundación segmental, o preferiblemente de inundación pulmonar completa, ha sido un tratamiento efectivo. La experiencia reciente ha demostrado que la inundación pulmonar completa puede ser efectiva, aún cuando la inundación segmental no ha sido tolerada o ha fallado.

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ANTIBODY RESPONSES IN SERIOUS BACTERIAL DISEASES A REVIEW

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The subject to be discussed really does not lend itself to considerations of practical and mundane matters like easy aids in diagnosis of infectious problems and their management. Rather it has been designed to review some of the things that the human body can and does do when invaded by viruses and bacteria and fungi—innate defensive events that assist the host in ridding himself of unwanted invaders. The topic, though, can help the physician understand the processes of infectious diseases and thus indirectly help him in his overall management of them. It might also elucidate why even bad therapies frequently are followed by clinical recoveries.

The human has a variety of built in defense mechanisms which are very effective. They are difficult to suppress, they rarely fail to be elaborated in the presence of microbial stresses, and on most occasions they are extremely powerful. *Without them,* such as occurs in patients with leukemia or lymphomas, and cirrhosis, any mild infection may become fatal. *With them* recovery is expected, even in severe infections, and without adjuvant antimicrobial therapy.

Responses to microbial invasion do not all happen at the same moment, some don't appear for several days, others are circulating and are active at all times. Thus an effort at describing the various responses in a chronological order seems sensible first, then will follow a review of recent advances in the area, using one kind of an infection to highlight the events.

Course of Infection in the Human

Irrespective of what health defects are present that permit a microbe to pass the body's first line barriers such as skin, intestinal and respiratory tract mucosa, to become implanted in a local body area, to multiply and spread therefrom, and to cause disease, these things happen in succession:

Following inoculation of the pathogen, (Table I) there is an almost immediate change in their number. For an hour or so they multiply rapidly, then abruptly and strangely, without overt evidence of local change, the numbers dwindle by as much as 75 to 90%. There obviously is something present in body tissues and/or blood that

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TABLE I: COURSE OF INFECTION FIRST SIX HOURS

(a remarkably stereotyped reaction)

First six hours: injury phase - the decisive period

A. Number of organisms increases initially; after 4th hour rapid decrease, then increase again.
B. Increased permeability of vascular endothelium with sludging of blood.
C. After 3 hours, beginning inflammation with diapedesis of leukocytes, increased vascularity of local lesion and induration.
D. Early activity of non-specific serum cidal substances.

acts as a cidal substance—natively present and in high concentration. As these accumulate with extraordinary rapidity at the injury site, there must be increased permeability of the blood vessels at this moment to permit their adequate concentration at that spot. The substances are multiple but most are not well described—histones, properdin, complement, endotoxin detoxifying chemicals, perhaps previously formed antibodies, and many others. Within 2 or 3 hours circulation in the area is altered with sludging of the cellular elements to the inner walls of vessels, then dilatation of these. Finally, but not before the third hour after implantation, actual inflammation begins with diapedesis of leukocytes, increased vascularity of blood and lymph, edema and induration. The numbers of organisms present at this time are less than present initially but soon thereafter, seemingly, they have adjusted to the killing substances and there is again a flurry of multiplication. If the patient is to survive, this explosion must be controlled.

Between the sixth and the 24th hour (Table II) other events come into play. Inflammation reaches peak intensity which is the body's attempt to contain the organisms in one area. Leukocytes begin to phagocytose, complement and other inbred cidal substances, particularly preformed antibodies, are used up—or almost—and new supplies of them are not yet available. Microbial drugs are exerting their maximal killing effects, thus restraining the aforementioned explosion of the bacterial population.

After the first day, (Table III) but before the third, there is demonstrated continued killing of microbes in the local lesion by drug, there is renewed production of the non-specific cidal substance and early clinical evidence of favorable change in the

TABLE II: COURSE OF INFECTION SIX TO 24 HOURS

(If no innate defense substances, organisms penetrate, spread and multiply)

A. Activation of preformed antibody.
B. Maximal activity of non-specific serum cidal substances as evidenced by fall in concentrations of complement and properdin.
C. Well established inflammation with macrophages and phagocytosis.
D. Maximal killing effect of antimicrobial agents.

TABLE III: COURSE OF INFECTION TWENTY-FOUR TO 72 HOURS

A. Rise above normal levels of properdin and complement and maximal agglutination of organisms.
B. Modification of antigens (from organisms) by macrophages (If too complete, particularly with therapy, no stimulation of R.E.S.)
C. Early changes in gamma globulins and proliferation of cells in R.E.S.
D. Clinical evidences of favorable change in disease pattern.

disease pattern. These occur if the patient is basically healthy, if his intrinsic defenses are not wanting, and if the original dose of bugs is not too great. If all of these factors do not obtain, there will be, by the second day, clear evidences of spread, of worsening of the clinical picture and of a life threatening situation, not likely ever to be changed without permanent tissue damage, even if the patient recovers. The antigens elaborated by the organisms for the first time are being altered by the macrophages. The lymph and plasma cells of the reticuloendothelial system are challenged by them to proliferate. This is accompanied by changes in concentration of the gamma globulin. If the macrophages alter too greatly the antigens, from the pathogens, and if the administered drugs have so reduced their numbers and production, the RES is not stimulated. There is subsequently no antibody production and cure may be achieved thereafter without them. This happens, for example, in the very early good treatment of streptococcal disease—no ASO titer rise happens and rheumatic fever does not supervene later. Similarly in typhoid fever, with early therapy, antibodies are not produced, but unless the drug treatment is prolonged, relapse results even after 30 days in many.

After the third day (Table IV) the body responses are directly related to the particular problem at hand, and all reactions are directed toward the eradication of the noxious microbe. Thus it takes the host at least 72 hours to respond directly to the invader, everything prior to this has occurred because he was born with non-specific substances only; they alone are never good enough for the final cure.

Interferons appear, in viral disease — these are antiviral protein materials in tissues

TABLE IV: COURSE OF INFECTION THREE TO SIX DAYS

A. Leveling of concentrations of non-specific defense substances, complement and properdin (Death in those who cannot respond with these).
B. Appearance of interferons (viral disease only).
C. Alpha globulin, fibrinogen and C-reactive protein rises; albumin falls.
D. Early rise in specific antibody with maximal activity of R.E.S.

and serum that interfere with the intracellular multiplication of viruses and are synthesized upon specific challenge of host cells. In bacterial disease alpha globulins rise, along with fibronogen, C-reactive proteins and specific antibody but the albumin falls. This period of maximal body response is truly crucial if eradication of the invaders is to be complete.

There begins the rapid clinical changes (Table V) with beginning resolution of the inflammation, the death of the majority of the pathogens and impressive changes in the plasma proteins, particularly the gamma globulins, which will be discussed later.

TABLE V: COURSE OF INFECTION SIX TO 14 DAYS

A. Antidoby (specific) reaches highest level.
B. B^2 (or gamma A) globulin rises with appearance of 19S (or gamma M) globulins.
C. Later (10 days) 7S (or gamma G) globulins appear.
D. Rapid clinical change toward normal with early resolutions of inflammation.

Finally, after the second week of infection, (Table VI) there comes the process of

TABLE VI: COURSE OF INFECTION AFTER SECOND WEEK

A. Properdin, complement, interferons, cidal substances returned to normal.
B. Rapid resolution of inflammation.
C. Total disappearance of pathogens.
D. Peak concentrations of 7S and 19S globulins (after 4th week 19S (g lm) decreases if infection subsides; and 7S persists).

clearing the products of inflammation—resolution hopefully, organization in any event. Should the initial invasion have been caused by a more slowly growing organism like the tubercle bacilli, the same chain of events develops, but the pace is slower. There is more tissue destruction and a much longer period is required in this final phases for resolution and organization. But the sequence is similar.

Protein Changes in Infection

In the past very few years there has been accumulated a remarkably large number of facts about the body's ability to produce specific antibody. If it does this properly, infection is eradicated, if it does not there is death; irrespective of antimicrobial therapy. Even the best of this latter treatment never sterilizes a lesion or cures a disease.

Antibodies are immunoglobulins which are the sole mediators of the immune reaction, formerly they were grossly classed as gamma globulins. There are at least 3 gamma globulins which have functional similarities but they are different structurally; all have antigenic specificity. The three have been assigned strange names and only recently has there been an attempt to make their classification internationally uniform. The original nomenclature was as follows: 85% of the fraction was labelled 7S because of its sedimentation constant. The second or macroglobulins with molecular weight of 1,000,000 were called 19S, also because of their sedimentation rate. The third group was also a 7S sedimenting protein with approximately the same molecular weight of ± 160,000 as the main group, but it had a separate kind of antigenic function and was called B_2A globulin or fast moving gamma globulin. The separation of these components of the gamma globulin part of plasma proteins was accomplished with perfection of the immuno-electrophoresis technique. As a result of studies with it the three have been renamed, as follows (Table VII): 7S = gamma G or Igg, 19S — gamma M or Igm and — gamma A or IgA. As noted

TABLE VII: IMMUNOGLOBULINS

Present Names	Proposed Names
Gamma, 7S, Gamma2, Gamma SS,	Gamma G or IgG
Macroglobulin, 19S B2M, Gamma M	Gamma M or IgM
B2A, Gamma A	Gamma A or IgA

in Table V, these immune substances appear in serum of infected people at the end of the first week, but at different times and in different amounts. Each is synthesized by a different clone of cells. The bulk of antibody is in the 7S or gamma G fraction. Gamma G globulins cross the placental barrier into the human fetus so that a baby is born with some of its mother's antibody. There is no gamma M (19S) or gamma A in the newborn. The mother's gamma G in the newborn is lost slowly in about 4-5

months, because the infant has quite immature plasma cells for stimulation during this period. Later, with stimulation, the child makes his own. Apparently gamma M (19S) antibodies are easier to produce and they are found in the 6 months old child. Both gamma G and M attain peak titers at 12 months, when the child finally becomes immunologically sophisticated with a fully active RES. The gamma A fraction becomes apparent only after age 12 years and are never seen before the 6th to 7th month of life.

In vaccination procedures with specific antigen, the gamma M (19S) appear first but decrease rapidly after 1-2 weeks, to be replaced gradually in 4-8 weeks by the gamma G group which persist. Much of the gamma G (7S) becomes extra vascular and in fact can be fixed in skin and tissues, the others can not, both staying in the circulation or in the case of gamma A in secretions like saliva.

The M proteins, such as those seen with myeloma are like the 19S group but none of these have antibody activity. The rheumatoid factor and auto-antibodies found in certain human ailments, like thyroiditis are also mostly macroglobulins, but their relationships with the others is unknown. It is probably true that the abnormal paraproteins like the Bence-Jones material are synthesized independently by plasma cells and in fact become incomplete gamma globulins molecules, but no one of them ever serves any useful function, in fact the opposite obtains.

To summarize the chain of events following implantation of micro-organisms: with it there is produced tissue injury, and phagocytosis commences with engulfment of foreign antigens, which are mostly protein like materials. These stimulate lymphoid hyperplasia with resulting enlarged local nodes, spleen and other parts of the RES. Such tissue then becomes a functional entity finally emitting the immunoglobulins at different speeds and in different concentrations. If the injury does not involve the exposition of foreign antigens, there is no lymphoid activation of antibody—or measurable increase in immunoglobulins. There is always needed, though, thoroughly competent cells in the system which can respond appropriately to any foreign stimulus by suddenly proliferating at an almost abnormal rate to produce substances which can neutralize the foreign protein invader.

Antibody is not ordinarily the total immunity of the host and as a whole they do not necessarily always protect the patient against the action of bacteria and their toxins, but they surely are an integral part of a host's defense against microbial injury and it is crucial that he have the ability to produce immunoglobulins.

Endocarditis as an Example of Protein Changes

With this brief review of antibody (or immuno-globulin) production as a defense mechanism—one disease can be taken as an example of what occurs during the course of a subacute and an acute bacterial disease. We have made a study of a small series of cases with endocarditis caused by streptococcus or staphylococcus with use of the indirect fluorescent antibody technic, and the results are applicable to this discussion.

Subacute endocarditis caused by a streptococcus either viridans or group D, is diagnosed generally several weeks after its onset Consequently, first observations are made

only after the body has had a chance to respond in a number of ways. In every case we have studied (10) the presence of gamma A, M and G globulins were noted to be at serum dilution levels of 1:640 or 1:2560

TABLE VIII: IMMUNOGLOBULINS STIMULATED BY ALPHA STRETOCOCCI IN PATIENTS WITH SBE

Immunoglobulins	Days after start of treatment		
	1	21	60
IgG	5*	5.	4.5
IgA	4.	4.5	3.3
IgM	3.	3.	2.

Number represents dilution of serum

(Table VIII) and were 16 to 64 fold higher than in a group of 10 normal healthy controls. As the disease progressed the gamma A and M concentrations gradually fell, the latter to almost zero, the former only slightly; G remained high for as long as 6 months. In one case the gamma G levels were low and rose later, the M globulins were very high initially, then fell during treatment. Although antibodies may have played a minor role in the patient's final cure, the body's response was classical. The observation as a matter of fact might be of real diagnostic value in determining the presence or absence of streptococcal disease in a patient with heart disease with fever whose blood fails to show bacteria in culture—which event happens in about 20% of cases of endocarditis. Similarly the fall or maintenance in concentration of gammas M and A may very well portend success or failure of treatment.

Contrariwise staphylococcal endocarditis is a very acute and morbid infection with

TABLE IX: IMMUNOGLOBULINS IN PATIENTS WITH STAPHYLOCOCCAL ENDOCARDITIS

Immunoglobulin	Days after start of RX		
	1	21	60
IgG	8	7	7
IgA	5	4	3
IgM	5	3	0

* Number represents dilution of serum Tube 1 — 1:10 2— 1:40 3 — 1:160 4 — 1:640 5 — 1:2560

an inordinately high death rate even with massive and good therapy. Diagnosis usually is made a few days after its onset. In one of our cases who survived, the immunoglobulin study was of interest (Table IX). The gamma G titers were very high at the time of diagnosis — yet the patient's disease was only about 4 days old when we first saw him. The M and A levels were also high — 4 to 16 fold greater than in a series of control subjects. As treatment progressed the G levels stayed at extraordinary heights — serum dilution 1:25,000. The patient recovered, and four months later all 3 immunoglobulins have fallen to control levels, M and A before G, and the M to zero. In acute infections then, utilization of the fluorescent technic to measure immunoglobulins can be used to determine prognosis — a worthy event indeed.

This small study is described merely to point out the practical aspects of studies of antibodies, or immunoglobulins during the course of human infections. In the instance of an abacteremic state, a few typical organisms like *S. viridans* and fecal streptococci can be used in the test of the patient's serum. Specific diagnosis without actually recovering the microbe from the patient

might well be possible with their sensible use.

Protein Changes in Other Infections Diseases

Virus and fungal pathogens do not stimulate the host to elaborate the immunoglobulin in the same fashion. In fact the initial injury phase is never so abrupt or acute, therefore the chain of events goes along at a totally different pace. In fungal diesease, for example, specific antibody as measured by the complement fixation test rarely becomes positive for 10 weeks and often not until after that. Despite their capacity to cause serious destructive damage to human tissue, fungal antigens are not capable of stimulating human immunoglobulin responses to the same order as do bacteria. And as could be predicted, by inference, fungal diseases are difficult to eradicate by any means. Although a similar pattern of human responses eventually obtain, the defense mechanisms, innate and produced specifically, must be considered quite inadequate in most fungal diseases, local or disseminated. This general statement applies to blastomycosis, actinomycosis, coccididomycosis, histoplasmosis and even to the dermatophytotic infections of the skin.

Responses contrariwise, to viral infestations are as prompt as with bacterial invaders, but never to the same degree. Changes in the alpha, beta and immunoglobulins are of low order, inflammation is less drastic and phagocytosis is never of an exciting nature. Nonetheless their presence prevents spread of viral progeny when they break out of one cell; they can't transfer to another. For this reason their presence alters favorably and specifically the course of the established disease, when they appear. They are of inestimably more value to the patient in his fight to control the disease, yet they are produced in lesser amounts than happens with bacterial disease.

Of more interest perhaps in viral disease and a major difference between them and other microbial infections, is the presence of interferons. These are protein substances that interfere with the development of the virus intracellularly. They are synthesized by many cells apparently (not just by RES cells) upon direct stimulation by the offending virus. When present they aid in altering favorably the course of viral disease in the human and have been demonstrated to do this in measles, polio, influenza and others. I wish we could elucidate the relationship between these and the immunoglobulins but I cannot. We can, though, anticipate exciting things about control of viral diseases as our information concerning them expands.

Final Discussion and Summary

It would indeed be convenient if studies of the immunoglobulins would ultimately lead to specific aids in both the diagnosis and to dependably beneficial treatment of microbial diseases in the human.

But this is not so with our present knowledge. What has evolved however is a far better understanding of the sequence of events that occurs in a diseased person. Eventually perhaps artificial enhancement of some parts of the changes may help. If we can ever do this it is logical to assume that we will be capable of aiding the diseased person to overcome and eradicate all microbial invaders. This happy possibility is not yet in the horizon. Neither in fact is the present information useful in prevention of infectious

ailments. As an analogy however, the discovery that insulin was manufactured in the pancreas was not immediately helpful to the patient with diabetes. It took two decades for the observation to become practicable. Perhaps we are now in the dawn or early morning of an era that can result in the achievement of a society free of, or safe from infectious disease. Comments today are solely for information. Further substantial achievements can soon be expected. In the meantime our best chance to control infectious diseases as we see them now are the wise and appropriate prescription of vaccines and chemicals, to help the human with proper mechanical barriers to prevent spread of disease and to keep abreast of more physiological knowledge concerned with body responses. Then we shall in fact have something new with which to dazzle tomorrow.

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CASE REPORT

PREGNANCY IN SHEEHAN'S SYNDROME

J.E. Rizek, M.D. and
Agustín M. de Andino, M.D.

Hypopituitarism of pregnancy* or Sheehan's syndrome is usually manifested by the sequential failure of the gonadal, thyroidal and adrenal functions. Occasionally only one or two of the target glands show evidence of insufficiency as a result of the pituitary destruction. Less frequently, some cases have been observed to recover normal function in one of the target organs. The resumption of menstruation after a period of amenorrhea is an uncommon occurence. More rarely patients with Sheehan's syndrome have become pregnant after the development of a full blown picture of panhypopituitarism. We have been able to collect only 20 cases after reviewing the medical literature.

Recently, we had the opportunity of observing a patient with the typical clinical picture of hypopituitarism of pregnancy who became pregnant five years after the diagnosis was made and who went on to deliver a normal full term baby girl.

It is the purpose of this paper to present this case and discuss some of the aspects of subsequent pregnancy in patients with Sheehan's syndrome.

Case Report

A 24 years old white female was first seen at the outpatient department of the San Juan City Hospital on August 30, 1956, complaining of epigastric burning pain, nausea, vomiting and frequent bouts of diarrhea. At that time a history of amenorrhea, weakness, loss of libido and scanty axillary and pubic hair was ellicited. The history dated back to March 3, 1956, when during the delivery of her 4th child she had a profuse intra and postpartum hemorrhage, went into profound shock and had to be rushed to a hospital where bleeding was arrested after manual extraction of a retained placenta. A transfusion of 1000 ml of whole blood was given to replace the blood loss. She recovered and was discharged nine days postpartum, but failed to lactate and following a scant hemorrhagic vaginal discharge, became amenorrheic. Loss of libido, diminution of axillary and pubic hair, and dyspareunia appeared gradually. She felt weak and developed epigastric burning pain, frequent nausea, vomiting and occasional diarrhea. From a pre-pregnant weight of 110 pounds she went down to 81. The past medical history revealed epileptic grand mal type of seizures during childhood, which dissapared spontaneously at the age of 18 years. The menarche occurred at the same age and the following cycles appeared regularly every 28 to 30 days, lasting 5

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* *The frequently used synonym "postpartum pituitary necrosis" implies that the pituitary lesion occurs only after delivery. For this reason we prefer the term* hypopituitarism of pregnancy *which includes all cases of pituitary necrosis occurring during the course of pregnancy. While there's good reason to believe that the pituitary gland is particularly vulnerable to anoxia during pregnancy, no specific complication is responsible for the syndrome and any condition associated with shock or anoxia during gestation may result in failure of the anterior lobe of the hypophysis.*

From the Section of Endocrinology, Department of Medicine, San Juan City Hospital, San Juan, Puerto Rico.

to 6 days. She had been married five years, pregnant four times and, except for the hemorrhagic episode mentioned, all pregnancies had terminated uneventfully in full term, normal spontaneous deliveries. She had breast-fed her three previous children.

The physical examination showed a thin, poorly nourished, pale, white female who looked chronically ill and appeared much older than her actual age. The temperature was 98ºF, the weight 81 pounds, the respirations 20 per minute, the pulse 62 per minute and the blood pressure 88 over 62 mm Hg. The neck was supple and the thyroid gland was not palpable. The chest was normal. The breasts were atrophic. Pelvic examination showed a small vagina with atrophic mucosa and a small retrodisplaced uterus. The skin was pale with loss of normal turgor. The axillary and pubic hair was absent. The scalp hair was diminished, thin and brittle. The rest of the physical examination was unremarkable. She was admitted for endocrine studies on February 23, 1957.

Laboratory studies showed a hemoglobin of 11.4 gm, a red blood cell count of 4.2 million per cu mm and a white blood cell count of 5,450 with 50% lymphocytes, 36% segmented, 2% stabs, 1% monocytes and 11% eosinophiles. The urinalysis was normal, the serology negative and eggs of *T. trichuria* were found in the stools. The serum total proteins were 6.1 with a normal partition.

TABLE I: DIAGNOSTIC STUDIES, 1956

Basal metabolic rate	35%
Serum cholesterol	231mg/100ml
I-131 uptake (24hrs)	13.2%
Urinary 17-ketosteroids	3.68mg/day
Serum Sodium	143mEq/
Serum potasium	4.88mEq/
Vaginal smear	Low estrogen activity

Table I shows some of the diagnostic findings. As is readily apparent, the was evidence of hypothyroidism, hypoadrenalism and hypogonadism. The chest x-ray showed a small heart and the skull series revealed a rather small sella turcica. Upper gastrointestinal series was negative. A gastric analysis showed the acidity to be decreased. The electrocardiogram showed inverted T waves in leads II, III and V-2 to V-5. Similar changes have previously been reported in hypopituitarism of pregnancy by Bernart and de Andino (1).

The glucose tolerance test shown in Figure I was flat with a tendency to late hypoglycemia.

Results of the Kepler's test are shown in Figure 2. The test was positive with decreased diuretic response to water loading.

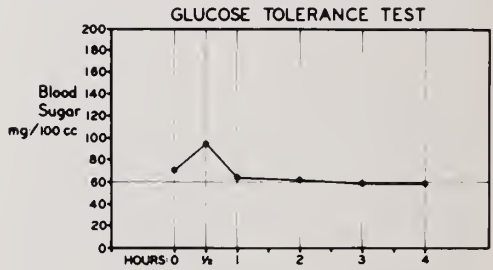


Fig. 1: Oral glucose tolerance test on patient on her initial admission to the hospital.

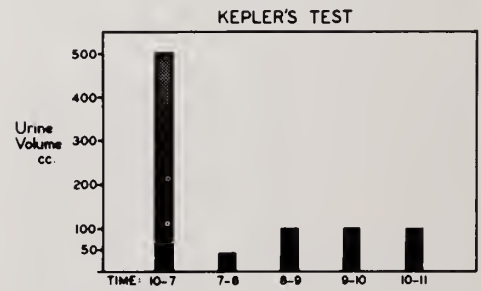


Fig. 2: Kepler's water loading test on admission.

The patient showed some improvement but complained of persistent weakness and gastrointestinal symptoms. She followed the treatment only at times because of socioeconomic problems. By 1959 she weighed 88 pounds, still felt weak and had epigastric symptoms. On September 1959 it was decided to start her on 12.5 mg of cortisone daily. In the following months the patient felt progressively better, weakness became less marked

and she began to gain weight. Epigastric symptoms decreased. At the end of 1960 her weight was maintained around 100 pounds and she had improved markedly. On March 3, 1961, at her regular clinic appointment, she complained of polyuria and morning sickness. She thought she might be pregnant. Gynecological examination was compatible with an intrauterine pregnancy of 10 weeks duration. Testosterone was discontinued but she continued taking 12.5 mg of cortisone and 120 mg of thyroid extract daily in addition to a modified dietary Sippy regimen. On October 10, 1961 she gave birth to a normal baby girl weighing 7 pounds and 13 ounces. The patient recovered uneventfully, but on her next clinic appointment she reported having had moderate vaginal bleeding 2 weeks after delivery. Her weight at that time was 104 pounds. Her condition has remained quite satisfactory since then with an almost complete return of pubic hair coupled with increased fullness of the breasts. In June, 1962 she noted scanty vaginal spotting for two days. A similar episode occurred on August, 1962. Ever since then she has not menstruated although she develops malaise, suprapubic discomfort and headaches at monthly intervals. When last seen on July, 1965 she was feeling well but complained of loss of libido and slight dyspareunia. She appeared comfortable, alert, well nourished and slightly older than her age of 33. Her weight was 112 pounds, her blood pressure 120 over 70 mm Hg and her pulse 76 beats per minute. The skin was dry. The breasts were pendulous but not atrophic. The vaginal mucosa was dry with some loss of normal rugae. The uterus was smaller than expected. The body hair was absent, the axillary hair markedly decreased with the pubic hair only slightly decreased. The deep tendon reflexes were normal. The sensorium was clear.

She was hospitalized on December, 1963 for re-evaluation. At that time the hemoglobin was 14.5 Gm, the red blood count was 4.65 million and the white blood cell count was 8,900 with a slight eosinophilia of 7%. The urine was acid with a specific gravity of 1.009. The fasting blood sugar was 85 mg per cent, the blood urea nitrogen 6.0 mg per 100 ml, and the serum sodium, potassioum, CO_2 content and chlorides were normal. The total proteins were 6.9 per 100 ml with 3.8 g of albumin and 3.1 g of globulin.

Endocrine studies revealed a serum cholesterol of 160 mg per 1000 ml, a protein bound iodine of 3.5 ug per 100 ml and a basal metobolic rate of minus 14 per cent. The vaginal smear showed moderate estrogenic effect. The results of the effects of ACTH and metopirone on the urinary excretion of 17-hydroxycorticosteroids and 17-ketosteroids are shown on Figure 3 and 4. These studies confirm the presence of persistent failure of the adrenocorticotrophic function of the pituitary gland.

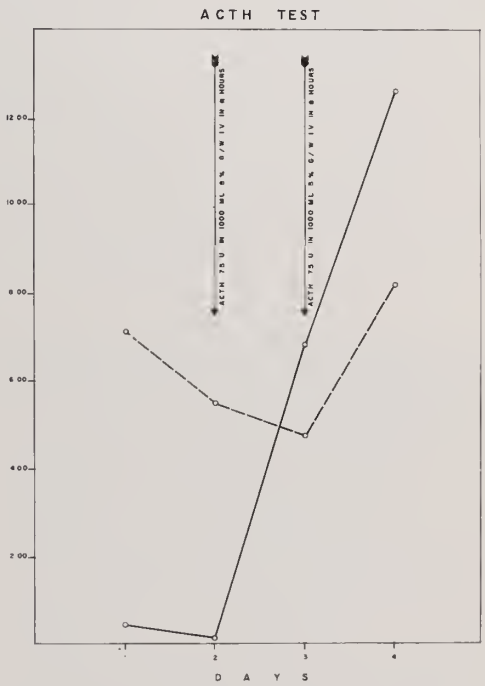


Fig. 3: Effects of intravenous ACTH on the urinary excretion of 17-ketosteroids (interrupted line) and 17-hydroxysteroids (continuous line) expressed in mg/day.

Gastrointestinal symptoms prompted this patient to seek medical advice. In the course of further examinations, she was found to be a case of hypopituitarism of pregnancy. No gastrointestinal pathology was found to ex-

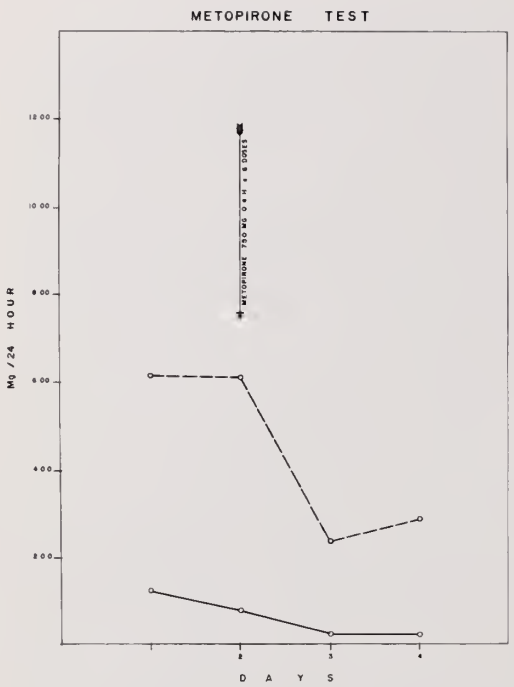


Fig. 4: Representation of the lack of response of the urinary 17-ketosteroids (interrupted line) and 17-hydroxysteroids (continuous line) to the oral administration of metopirone.

plain her symptoms. In spite of the institution of an ulcer regime, she did not show evidence of improvement. When cortisone was added to the therapeutic plan, there was general improvement and a slow disappearance of her abdominal complaints. It is obvious that the presenting picture of epigastric distress, burning, nausea and vomiting was a manifestation of adrenal insufficiency, which responded promptly to substitution therapy. Her subsequent pregnancy occurred at the time when she was asymptomati and her general condition approached her previous normal state of health. The reappearance of gonadal function has been reported in the literature occasionally (2, 3, 4, 5).

In the cases with return of normal menses, manifestations appeared mainly when substitution therapy was instituted. In some, the omission of hormonal treatment was repeatedly followed by recurrence of the amenorrhea (3). Our patient probably behaved in a similar manner. Although she never menstruated, she obviously ovulated when she became pregnant, but one can not be certain as to whether ovulations had occurred in the previous four years of her disease. However, she had continued her marital relations regularly ever since the time of her fourth delivery, and we may postulate that she was not fertile during that period of time.

Subsequent pregnancies in cases of Sheehan's syndrome are uncommon (2, 4, 5, 6, 7, 8, 9, 10, 11, 12). According to Sheehan, when they do occur, they seem to be beneficial to the general condition of the patient (2). He has advocated the encouragement of further pregnancies, when possible, based on the theory that improvement might ensue provided the pregnancy proceeds and terminates uneventfully. Though several cases of such occurrence have been documented, it remains to be determined if this is truly a correct assumption. Murdoch et al (4), on the other hand, state that the improvement brought about by subsequent pregnancies lasts only as long as the pregnant state and that patients again lapse into full hypopituitarism after delivery. In either case, it seems that in some cases partial or complete recovery of endocrine function can be achieved by improvement of the patient's general condition with adrenal and thyroid replacement. While in the classical case of hypopituitarism of pregnancy the patient notices first the symptoms of hypogonadism,

it is our impression from observation of sixty five cases of the syndrome, that this does not necessarily mean that the gonadal function is the first one to fail. While a woman will promptly notice amenorrhea and seek medical attention for it, she may not be aware of the protracted symptoms of mild or moderate hypothyroidism or hypoadrenalism until these have progressed and caused a general derangement of her health. This may lead to amenorrhea, perhaps aided by a partial decrease in the gonadrophic function of the pituitary gland. At this stage, as Sheehan (6) has pointed out, the patient may be mentally too dull to report for medical treatment. It is almost impossible to tell clinically which patient may have some remaining gonadotrophic activity, as gonadotrophin levels do not correlate well with the clinical evaluation. Therefore, it is our impression that everything should be done to improve the patient's general health and that optimum endocrine function be achieved by adequate replacement therapy, in order to give the patient the best chance for recovery of gonadal function.

Summary

A case of Sheehan's syndrome (hypopituitarism of pregnancy) who became pregnant five years after the onset of her disease is presented and some of the clinical aspects of the condition are discussed.

Pregnancy following hypopituitarism is rare. However, when it occurs it seems to be beneficial to the patient. Since there is always a possibility that the patient may recover some gonadal function when her general condition is optimal, every effort should be made to achieve normal health by adequate replacement therapy of whatever endocrine and non-endocrine deficiencies are found.

Resumen

Se presenta un caso de síndome de Sheehan (hipopituitarismo de embarazo) con un embarazo subsiguiente a los cinco años de enfermedad. Se discuten algunos aspectos clínicos de este síndrome.

La aparición del embarazo después de hipopituitarismo es rara. Sin embargo cuando ocurre parece ser beneficioso para la paciente. Como siempre existe la posibilidad de que la paciente recobre parte de su función gonádica cuando su condición general es óptima, debe hacerse un esfuerzo por proporcionar a la enferma la mejor salud posible por medio de la terapia sustitutiva de las deficiencias endocrinas y no-endocrinas que afectan al paciente.

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EDITORIAL

POISON PREVENTION WEEK

The week of March 20-26, 1966 has again been set aside by Presidential Proclamation as Poison Prevention Week. The Governor of Puerto Rico through the office of The Secretary of Health has also officially proclaimed this week to alert all of us to the many possible dangers of poisoning in our everyday life.

Poisoning is a horrible and terrifying crisis that can be avoided and every effort must be made in this direction.

Not since the "middle ages" has poisoning been such a problem as it is today. Today's problems however are different; accidental poisonings are now most frequently encountered. Can it be because of the increase in the population or a greater awareness of poisoning, or is it the ever increasing number of household products (time and labor savers) that find their way into our homes. "Better and more leisure living through chemistry" also has its hazards. Chemicals to kill weeds or insects, furniture polish, or the wonder drugs when taken or used in a wrong manner can be dangerous and deadly.

It has been estimated that at least several hundred thousands children in the United States(1) are brought to their physician yearly because of the possibility of poisoning exists. Fortunately most of these children survive, though survival is not always the only consideration. The child may be left with a permanent damage, mental retardation or phisical disfiguration. Poisoning in children are most frequent between the ages of 1 and 5 and more are killed in this age group than by diphtheria, polio, measles and whooping cough combined.

The week of March 20-26, 1966, is then to be set aside as a reminder to survey and to clean out certain areas in our homes such as medicine cabinets under the kitchen sink, the garage and any other place of storage and to discard all unnecessary chemicals or drugs. The ones kept should be labeled clearly and stored in a safe place. All *chemicals and drugs are dangerous when in the sight and reach of a child. Phisician's children* are not exempted; *they are especially exposed more often and to a larger variety of drugs which carelessly may be left around the home.*

It is an endless task, constantly warning the mother to minimize this hazard. The vast majority of these accidents occur at home while the mother

is at home. Much grief can be avoided if only we could follow a few common sense rules such as:

1. Keep all pesticides, drugs, chemicals, cleansers, etc. out of sight and reach of children. Watever is in sight they will try to reach. Parathion-like insecticides are the number one killer in Puerto Rico.

2. Do not store any *non edible products on shelves used for storing food.*

3. Keep all products in their original *containers and do not transfer to a "soft drink" bottle, or an unlabeled or mislabeled container.*

4. When medicines are discarded, do it thoroughly. Do not throw them where they can be reached by children or pets.

5. When giving flavored and/or colored medicines to children, never *call it candy.*

6. Do not ever take drugs in the dark. Read labels before using, and use only as prescribed.

The very fact that the above list"sounds silly;" and further more that "it can't happen to me" is the main purpose of this short communication.

Once a poisoning does occur (as it will, in spite of preventive measures), speed in diagnosis is an important factor in effective treatment. Diagnosis is not always easy. It is urgent to know the toxic ingredients. Read the label, it may or may not contain this information.

After attending to the immediate emergency (symptomatic and supportive), a history of circumstances should be solicited from the family. The police, public health nurse or sanitarian at the District Hospital can be of great assistance in this regard.

A correlation of signs, symptoms, odors and other clues may be of value.

The following, although not specific may help to rule certain possibilities in or out:

Coma: Alcohols, Barbiturates, Bromides, Hypnotics, Antihistamines.

Convulsions: Strychnine, camphor, parathion group.

Dilatation of pupils: Belladonna group, epinephrine group, amphetamines etc.

Constriction of pupils: Morphine group, parathion group.

Cyanosis: Nitrites, chlorates, aniline derivatives.

Acidosis: Methyl alcohol, salicylate group (Aspirin).

Tachycardia, bradycardia, rapid breathing, slow breathing, Cheyne-Stokes respiration, perspiration, dry throat, liver involvement, kidney damage, blood dyscrasia, etc., all would be of help in the diagnosis(2).

Also the immediate use of rapid presumptive testing for at least some of the more common poisons would be of assistance(2).

Since it is impossible for the busy practitioner to be familiar with the thousands of possible toxic agents, ingredients, commercial names, their effects

on humans, signs and symptoms and proper treatment and management, Poison Control Centers have been established in the various District Hospital of Puerto Rico to assist whenever they can.

These Poison Control Centers have begun in a modest fashion and they already have been expanding as experience and need requires. These centers and their services are a result of the wholehearted enthusiasm and cooperation of each of the District Hospitals and their personnel who are giving of their time and efforts in addition to their other regular duties.*

**The location of these Centers is listed under Noticias (Locales).*

Sidney, Kaye, Ph. D.

1. National Office of Vital Statistics
2. *Kaye, S.*: Handbook of Emergency Toxicology: A Guide for the Identification, Diagnosis and Treatment of Poisoning. C.C. Thomas, 2nd Ed., Springfield, Ill.

Niveles Económicos y Enfermedad Arteriosclerótica del Corazón

En un estudio (1) poblacional publicado recientemente sobre la incidencia de enfermedad de las arterias coronarias en Estados Unidos, se encontró una relación inversa entre los ingresos de la familia y la incidencia de enfermedad arteriosclerótica del corazón. Entre los varones cuyas familias tenían un ingreso anual sobre $10,000, la incidencia fué de aproximadamente la mitad de la hallada entre los menos afortunados económicamente. Este hallazgo es contrario a la idea prevaleciente de ser esta una enfermedad más de las clases pudientes. Resultados parecidos se han descrito en Inglaterra (2) y entre los empleados de una gran planta industrial norteamericana (3).

Estos estudios indican la necesidad de una más detallada investigación para mejor dilucidar los factores patogenéticos en esta importante enfermedad.

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Eradication of Tuberculosis

The following resolution prepared by a joint committee composed of representatives of the American College of Chest Physicians and the Committee of the Section on Diseases of the Chest of the American Academy of Pediatrics, has been approved for publication by both Societies:

WHEREAS, Tuberculosis now causes the illness of approximately 20,000,000 people and the death of 3,000,000 people in the world annually, and

WHEREAS, It results in more incapacity and death than the other communicable diseases combined, and

WHEREAS, Eradication of tuberculosis must begin with the prenatal period when the environment into which infants are to be born is made free from communicable cases of tuberculosis, and

WHEREAS, Every effort should be made to maintain this environment during the preschool and school years, and

WHEREAS, The Committees on Tuberculosis in the schools, colleges and universities throughout America should receive the unqualified support of all physicians and tuberculosis organizations in order to maintain an environment free from communicable cases of tuberculosis not only in the schools and colleges, but also in the homes and communities, and

WHEREAS, A program providing that all present children be tested with tuberculin, that those not yet infected be protected from

infection from tubercle bacilli and that those now infected be treated with well-known methods to prevent them from developing tuberculous complications during childhood and possibly from developing destructive clinical lesions later, would speed up the elimination of tuberculosis, and

WHEREAS, All necessary procedures are now available to accomplish this goal,

THEREFORE, BE IT RESOLVED, That the American College of Chest Physicians and the American Academy of Pediatrics recognize the importance of this program and urge all of their members to support and take part in these activities, and

BE IT FURTHER RESOLVED. That this Joint Committee recommend and urge the members of the two organizations represented to adopt and vigorously promote a program to guarantee an environment free from tubercle bacilli for our infants and children, and

BE IT FURTHER RESOLVED, That this Joint Committee recommend that our respective organizations urge all other groups of physicians, especially obstetricians, general practitioners and health officers, to join in the nationwide endeavor to protect children against the hazards of tuberculosis.

Tuberculin Skin Testing of Children

By a joint committee of the Section on Diseases of the Chest of the American Academy of Pediatrics and the American College of Chest Physicians.

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Infection with tuberculosis in children is still a problem. Since early treatment with INH has been found valuable for tuberculin converters, particularly in the very young, it is mandatory that tuberculin testing be carried out early in life. This Committee strongly suggests that routine tuberculin testing be initiated between 6-12 months of age, preferably before measles or smallpox vaccination, and be repeated annually up to 4 years of age and thereafter every 2 years, depending on the risk of exposure of the child and the prevalence of tuberculosis in the population group. To this end the following recommendations are made:

(1) The Mantoux Test is the most accurate measure of tuberculin sensitivity. Intermediate P.P.D. (5T.U.) is the standard test dose. The reaction to the Mantoux is read on the second or third day. The diameter or induration should be measured and recorded. Ten (10) mms. or more of induration indicates a positive reaction and 5-9 mms. induration is considered a doubtful test.

(2) For clinical screening a multiple puncture test may be employed. (e.g Tine, Heaf). Any doubtful reactions should be checked by Mantoux testing.

(3) The use of tuberculin patch tests is not recommended.

(4) PPD when diluted in quantities of 50 doses or more may be stored for periods of up to 6 months without significant loss of potency provided the material is kept refrigerated, sterile and away from sunlight.

* Retorno a la Práctica de Enfermería Clínica

Lo siguiente es una cita de un artículo publicado en un número reciente del JAMA (1).

"Currently in some centers, the employment of unit managers and other nonnursing persons to perform the nonprofessional activities now being done by nurses is being instituted. Those tasks necessary to keep the hospital functioning should be rightly an extension . of hospital administration and not of nursing. While it is a small beginning, it has not been pushed far enough nor fast enough to relieve most nurses of the functions which divert much time from nursing care. Doctors and nurses working together and insisting on organizational structures that free the time of nurses to work with patients would greatly improve care in a relatively short space of time. With proper utilization of registered nurses, two to three times the present supply of nursing manpower would be available without training another nurse. This means that the number of auxiliary personnel could be greatly reduced or their use eliminated. Pellegrino (14) has written a highly suggestive paper about the outcome of such a move. Nurses will need the persistent support and assistance of physicians as they attempt to develop a high level of clinical practice with patients.

A major move of this type would call for reorganization of the nursing department. A much simpler structure, with less stratification, would probably serve nursing best. One way to achieve this goal would be to organize nursing in a pattern similar to the one utilized by medicine, that is, to institute a surgical nursing staff with a chief of surgical nursing, and so on for all the specialty areas. The director of nursing would be selected for clinical competence. He or she would work closely with the medical chief of staff in developing improvements in patient care. With both groups having similar perceptions of clinical practice, there would be more congruence in the manner of giving care and less disturbance in the communication channels between each group and each practitioner. The cognitive backgrounds of nurses and physicians would be more nearly similar, and, therefore, communication should be easier. The bonus in improved patient care that could come from an organizational arrangement such as this might be spectacular.

Nurses are showing a greatly increased interest in clinical practice. The House of Delegates of the American Nurses' Association at its last convention voted to explore the feasibility of establishing clinical board specialties. This movement is in a budding stage. A shove from combined organized medicine and nursing could bring it into full bloom. Expert nurse clinicians could increase the ease and accuracy of communication between the two disciplines. The nurse specialists, in addition to working closely with their medical colleagues, could act as consultants on expert practice to the remainder of the nursing staff. The nurse specialists could have the same effect on nursing practice as the medical consultants have had in raising the level of the practice of medicine. The discrepancies in perception of the patient-care process between physicians and nurses should be lessened.

At the last American Nurses' Association convention it also was voted to establish, as soon as possible, baccalaureate education as

the educational foundation for professional nursing. With the phenomenal expansion of medical knowledge this seems to be the form of education that can keep pace best with that of physicians. It is the only form that readily lends itself to continuing education. Again, the organized support of medicine and nursing could bring into actuality an enlarge body of skilled nurse practitioners. Since these nurses would have a substantial amount of training in the basic sciences from which both groups derive the basis for practice, the need for message clarification between groups should be reduced. A technical nurse seems to be evolving out of the junior-college programs. The reduction of nursing categories to one technical and one professional should assist in clearing communication channels because the nursing structure would be simplified and the levels of training more fully understood."

References

1. *Christman, L.P.:* Nurse-physician communications in the hospital. JAMA 194:539, 1965.
14. *Pellegrino, E.D.:* The changing role of the professional nurse in the hospital, Hospitals 35:56-62, Dec. 16, 1961.

Uterine Cervical Cancer and Poverty

Scientists of the Public Health Service and University of Louisville have found evidence supporting a long-held belief that the risk of uterine cervical cancer is considerably higher among the poor.

The findings were reported in the December issue of the *Journal of the National Cancer Institute* by Dr. Frank E. Lundin, Jr. and Winifred M. Mendez, National Cancer Institute, National Institutes of Health, and Drs. William M. Christopherson and James E. Parker, University of Louisville School of Medicine.

The collaborative study, which was supported in part by a contract from the Public Health Service, U.S. Department of Health, Education, and Welfare, involved nine years of community-wide testing for uterine cervical cancer among women in Louisville and Jefferson County, Kentucky. During this interval, more than 413,000 "Pap smears," specimens of cells obtained from the vagina, were examined with a microscope.

Two findings stand out in this study. In Louisville, the number of new cases of invasive cervical cancer for each 100,000 women ranged from 25 for the highest socioeconomic area to 63 for the lowest income area. Among women living outside the city limits, in general an upper-income area, the number of cases was about 27 per 100,000.

Furthermore, as the study progressed, more cases than expected were found in early stages, which are more responsive to curative treatment.

The scientists suggest that, "It would thus seem that, if a substantial decrease in morbidity (illness) from this disease is to be accomplished, one should concentrate on, or at least give some priority to, the cytologic examination of... underprivileged...women."

Eye Infections From Puppies and Kittens

The protection of children's eyes is another good reason for de-worming puppies and kittens, suggests an article in the current (December 27) Journal of the American Medical Association.

The report tells of a 6-year-old girl who never went near dogs or cats, but nonetheless

suffered blurred vision and inflammation in one eye for more than a year. At some earlier time, she apparently had swallowed dirt infested with the eggs of Toxocara canis, the common dog roundworm.

The larva probably got into the girl's bloodstream, and was carried to the peripheral retina area of her eye. It lived on, healthy and vigorous.

As the *report points out, kittens and puppies,* not mature dogs and cats, are more likely to spread such infections to people of all ages. Adult cats and dogs are less likely to transmit the disease because previous infections may have established immunity to reinfection and recycling of the larvae.

A tragic part of the story is that the girl died about a year later, of causes unrelated to the eye condition. During that year, however, three physicians at the University of California's San Francisco Medical Center were able to follow the case closely.

As a Journal editorial notes, their report is of considerable importance because of the unusual location of the larva, the opportunity to follow the case for such a time, and because this is but the second reported T. canis infection of the pheripheral retina area.

Such infections may be fairly common, however. "In a recent survey of the types of uveitis (infections of the colored portion of the eye) it was found that 16 per cent of cases suffered from an inflammation similar to the one reported," said the Journal editorial.

Of these, about 25 per cent (four per cent of the total) had an inflammation in only one eye. Larva infections seldom affect both eyes.

"If this four per cent all had ocular nematodiasis (eye infections from worms), the disease must be fairly common in this country," the editorial said.

"How is the public to be informed about the need for de-worming young puppies and kittens, so they do not shed ova which can be ingested and lead to human disease?" asked the editorial.

"Too little publicity has been given to the problem by health authorities. Parents are largely unaware of the danger created by infected puppies and kittens in a neighborhood. Veterinarians should be in the vanguard in the dissemination of information about the proper care of young animals," the editorial said.

Authors of the Journal article are Michael J. Hogan, M.D., Samuel J. Kimura, M.D., and William H. Spencer, M.D., all of the Francis I. Proctor Foundation for Research in Ophthalmology and the Department of Ophthalmology, University of California, San Francisco Medical Center.

American Academy of Pedriatics

Children Should Be Tested Early For TB

The American Academy of Pediatrics and the American College of Chest Physicians have recommended that all children between the ages of 6 and 12 months of age be tested for tuberculosis.

The tests should be given, if possible before the child has been vaccinated against measles or smallpox.

The recommendations of the two organizations were made in a joint-committee statement appearing in the current, (Jan. 1) issue of the AAP's *News Letter.*

The Committee emphasized that tuber-

culous infection in children is still prevalent, and that testing for tuberculosis should be "repeated annually up to 4 years of age and thereafter every 2 years, depending on the risk of exposure of the child and the prevalence of tuberculosis in the population group."

The Committee noted that early treatment of tuberculosis with the drug, isoniazid, has been especially effective in young children.

In an earlier statement, the two organizations urged their members and other groups of physicians including obstetricians, general practitioners, and health officers to "join in the nationwide endeavor to protect children against the hazards of tuberculosis."

The statement noted that children infected with tuberculosis should be "treated with well-known methods to prevent them from developing tuberculous complications during childhood."

The statement indicated that such testing and treatment would "speed up" the elimination of tuberculosis, and that "all necessary procedures are now available to accomplish this goal."

Tuberculosis annually infects approximately 20 million people throughout the world, resulting in death for some 3 million people each year.

The American Academy of Pediatrics, with headquarters in Evanston, Ill., is the Pan-American association of physicians certified in the care of infants, children, and adolescents.

The Academy has more than 9,100 members in the U.S., Canada, and Latin America.

CARTAS

El Tratamiento de Muerte Repentina

El tema de "muerte repentina" es usualmente alejado de nuestro pensamiento. Es un tema desagradable. Preferimos ni tener que considerarlo en nuestro trabajo diario. Sin embargo, ocurre con apreciable frecuencia y, en ocasiones, en forma inesperada y sin causa aparente.

Los médicos sabemos que la muerte clínica *puede* ser reversible. Durante los últimos años esto se ha demostrado repetidamente. Mediante la *pronta* y *eficiente* ejecución de las "nuevas" técnicas de resucitación cardiopulmonar, *es posible* ofrecer una segunda oportunidad a muchas víctimas de "muerte repentina." El énfasis está en *prontitud* y *eficiencia* en el tratamiento. Para esto es necesario un plan de acción sencillo, pero eficiente, pues la muerte repentina no escoge hora o sitio. Para que el tratamiento tenga más posibilidades de éxito, es la persona más próxima a la víctima la llamada a *iniciar* el tratamiento con prontitud y eficiencia. Solamente se dispone de tres a cinco minutos antes de que la muerte clínica (reversible) se convierta en muerte biológica (irreversible).

El método de resucitación cardiopulmonar por compresión externa del corazón y respiración boca a boca debe considerarse un procedimiento *de emergencia* para ser utilizado por *cualquier persona capacitada* que haya recibido entrenamiento en estas técnicas.

Todo médico debe considerar su deber aprender, practicar y *enseñar* las técnicas de resucitación cardiopulmonar al mayor número de personas capacitadas posible.

Las Facultades Médicas de los distintos hospitales deben preocuparse más por este tema. Es a través de los hospitales que se logrará una mayor difusión de estos conocimientos y el entrenamiento de todas aquellas personas capacitadas para aprender los mismos.

Todo hospital debe ofrecer el máximo de seguridad posible a sus pacientes. Personal entrenado en resucitación cardiopulmonar y un plan de acción ya establecido, sin duda alguna, contribuiría a lograr este objetivo.

M. A. Colón-Morales, M.D.

NOTICIAS

Locales

BOLETINES VIEJOS

La Asociación Médica de Puerto Rico está interesada en obtener copias de los siguientes números del Boletín:

Año	*Meses*
1920	enero a diciembre
1922	enero a diciembre
1923	enero a diciembre
1925	enero a diciembre
1927	enero a diciembre
1928	enero a diciembre
1942	enero a diciembre
1943	enero a diciembre
1944	enero a diciembre
1953	abril, junio y agosto
1957	agosto
1962	julio

Aquellos miembros de nuestra matrícula que tengan estos volúmenes y deseen donárselos a la Asociación Médica, favor de comunicarse con el Sr. Eulogio Bermúdez Vélez, Secretario de Redacción.

OPORTUNIDADES DE TRABAJO PARA MEDICOS

1. Hemos recibido notificación del Fuerte Brooke en San Juan expresando la disponibilidad de oportunidades de trabajo para médicos en la oficina de exámenes de las Fuerzas Armadas en el Fuerte Brooke, San Juan. Para información adicional se puede llamar al Capitán P. J. Alamo, teléfono 722-4000, extensión 3280, Fuerte Brooke.

2. El Sr. Tomás E. Alcalá Gómez, Director de la División de Corrección del Departamento de Justicia, nos informa que la Administración de Instituciones Penales tiene un puesto vacante de Médico 5, Director Médico, en la Penitenciaría Estatal. Los interesados pueden comunicarse con el Sr. Alcalá Gómez en el Departamento de Justicia.

Feb. 22-26, 1966 — Convención Anual del Capítulo de P. R. del Colegio Americano de Cirujanos

CONGRESO NACIONAL DE ETICA MEDICA Y PROFESIONALISMO

El Dr. Luis F. Sala, Presidente de la Asociación Médica de Puerto Rico, ha designado al Dr. Carlos Quilichini, quien Preside el Comité de Etica de la Asociación Médica de Puerto Rico para que represente a nuestra Asociación en el Congreso Nacional de Etica Médica y Profesionalismo que auspicia la Asociación Médica Americana. Dicha actividad se celebrará en la ciudad de Chicago en marzo de 1966.

CURSO POSTGRADUADO

El American College of Chest Physicians está ofreciendo un curso Post-Graduado durante los días 21, 22 y 23 de marzo en el Hotel La Concha. Distinguidas personalidades del continente y del extranjero además de miembros de la Facultad de nuestra Escuela de Medicina y del Hospital Dr. A. Ruiz Soler y otros hospitales tomarán parte activa en el mismo. Los médicos interesados deberán informarlo al Dr. Guillermo Acosta, Presidente de la Sección de Enfermedades del Pecho, de la Asociación Médica de Puerto Rico y del Capítulo de Puerto Rico, del American College of Chest Physicians.

Dirección:
Hospital Dr. A. Ruiz Soler
Bayamón, Puerto Rico
Teléfono 782-0120

Próximamente circulará el programa.

Abril 25-29, 1966 — Primer Congreso de Medicina

Física y Rehabilitación del Caribe, Hotel San Juan, San Juan, P. R.

CONGRESO MUNDIAL DE MEDICINA DEL DEPORTE

El Comité Olímpico de Puerto Rico a través de su Presidente, el Sr. Felicio M. Torregrosa, nos informa sobre la celebración del XVI Congreso Mundial de Medicina del Deporte que se celebrará en Hannover, Alemania Ocidental, durante los días 12 al 16 de junio de 1966. Cualquier interesado puede obtener mayor información comunicándose con las oficinas centrales de la Asociación Médica de Puerto Rico.

PREMIOS DOME LABORATORIES

Dome Laboratories anteriormente Dome Chemicals, Inc., de Nueva York ha establecido por intermedio del Colegio Ibero Latinoamericano de Dermatología (CILAD), dos premios de 800 dólares el primero y 400 dólares el segundo para los mejores trabajos originales de investigación no publicados previamente y relativos a algún aspecto fundamental de la dermatología. Se otorgará además diploma y medalla a todos los firmantes de los trabajos premiados.

Los trabajos deben ser escritos en Idioma Español o Portugués.

Los trabajos para optar al premio deben ser presentados al VI Congreso Ibero Latinoamericano de Dermatología.

Este primer concurso se cerrará el 31 de octubre de 1966.

Para informes más detallados sobre las condiciones del concurso, favor escribir a:

Dr. David Grinspan
Arenales 947 - 2º A
Buenos Aires, Argentina

DISTRICT POISON CONTROL CENTERS

The following have been designated District Poison Control Centers of Puerto Rico.

1. San Juan Municipal Hospital
   Dr. Osvaldo González Alvarez, Director
   Tel. 724-7002
   Centro Médico, Río Piedras
2. Ponce District Hospital
   Dr. Luis A. Rosario, Director
   Emergency Room
   Tels: 842-2080; 842-2048
3. Arecibo District Hospital
   Dr. Jesús Rodríguez García, Director
   Tel. 878-3535, Ext. 31
4. Fajardo District Hospital
   Dr. Rubén Ramón, Director
   Tel. Nº 566
5. Aguadilla District Hospital
   Dr. Herminio Aluarel, Director
   Tel. 791-0200
   Dr. Pedro Mendoza, Asst. Director
   Tel. 791-0200
   Aguadilla District Hospital
   Dr. Sidney Kaye
   Professor of Toxicology and
   Legal-Medicine
   Coordinator for The Health Department.
   Institute of Legal-Medicine
   Escuela de Medicina, U.P.R.
   Tel. 765-0615; 765-4880, Centro Médico
   Río Piedras, P.R.

Nacionales

Feb. 21-25 CANCER, Presbyterian-St. Luke's Hospital, Chicago, III.; Samuel G. Taylor, III, M. D., F.A.C.P., Director.

Mar., 7-11 THE BIG HEART, Cardiac Work and Cardiac Hypertrophy: Clinical Appraisals, Therapeutic Considerations and Pathologic Correlations, Baylor University College of Medicine, Houston, Texas; Raymond D. Pruitt, M.D. F.A.C.P., Director.

COURSE IN LARYNGOLOGY AND BRONCHOESOPHAGOLOGY

March 21 to April 2, 1966. The Department of Otolaryngology of the Illinois Eye and Ear Infirmary and the College of Medicine of the University of Illinois at Medical Center, Chicago, will conducts a postgraduate course in Laryngology and Bronchoesophagology. This course is limited to fifteen physicians and will be under the direction of Paul H. Holinger, M.D. It will be held largely at the new Illinois Eye and Ear Infirmary, 1855 West Taylor Street, Chicago, and will include

visits to a number of Chicago hospitals. Instruction will be provided by means of animal demonstrations and practice in bronchoscopy and esophagoscopy, diagnostic and surgical clinics, as well as didactic lectures.

Interested registrants will please write directly to the Department of Otolaryngology, College of Medicine of the University of Illinois at the Medical Center, Postoffice Box 6998, Chicago, Illinois 60680.

Mar. 28 - April 1. BASIC MECHANISMS IN INTERNAL MEDICINE, University of Toronto, Toronto, Ontario, Canada; K. J. R. Wighaman, M.D., F.A.C.P., Director.

April 14-16. CURRENT CONCEPTS OF RENAL, GASTROINTESTINAL AND CIRCULATION PHYSIOLOGY, co-sponsored by the American Physological Society, Barbizon-Plaza Hotel, New York, N.Y.; Daniel H. Simmons, M.D., F.A.C.P., and Charles Kleeman, M.D,, F.A.C.P., Co-Directors.

April 25-28. The 1966 American Industrial Health Conference, will be held in Detroit, Michigan, with headquarters at the Sheraton Cadillac Hotel and meetings in Cobo Hall, it has been announced by the INDUSTRIAL MEDICAL ASSOCIATION and the AMERICAN ASSOCIATION OF INDUSTRIAL NURSES. This medical-nursing Conference which is comprised of the annual meetings of the two sponsoring Associations, will bring together approximately 2,000 persons which, in addition to industrial physicians and nurses, will include industrial hygienists, safety engineers, public health officials, military service medical personnel, university faculty members, management representatives and others who have an interests in the health of the working population. The annual meeting of the Industrial Medical Association will mark the organiaztion's 50th anniversary meeting.

The scientific program, in which many of the nation's experts in the field of occupational health will participate, will be augmented by both scientific and technical exhibits. Intensive courses in selected areas of medical practice also will be presented. Further information about the Conference may be obtained by writing American Industrial Health Conference, 55 East Washington Street, Chicago, Illinois 60602.

May 9-13. INTERNAL MEDICINE IN LIGHT OF RECENT DEVELOPMENTS, Pennsylvania Hospital, Philadelphia, Pa.; Garfield G. Duncan, M.D.; F.A.C.P., and Robert J. Gill, M.D., F.A.C.P., Co-Directors.

May 16-20. PHYSIOLOGICAL ASPECTS OF CARDIOPULMONARY DISEASE, Indiana Univ., Indianapolis, Ind.; John B. Hickman, M.D., F.A.C.P., Director.

May 23-25. NATIONAL TUBERCULOSIS ASSOCIATION. The 1966 Annual Meeting of the American Thoracic Association will be held in San Francisco, California.

June 13-17. ADVANCED PSYCHIATRY FOR INTERNISTS, Baltimore Psychoanalytic Institute, Baltimore, Md.; Ephraim T. Lisansky, M.D., F.A.C.P., Director.

June 15-18. NEUROLOGY FOR THE INTERNIST, Bowman Gray School of Medicine, Winston-Salem, N.C.; James F. Toole, M.D., F.A.C.P., Director.

Internacionales

Curso Completo de Gastroenterología para Graduados

A partir del 4 de marzo de 1966, se encontrará abierta la inscripción en el Departamento de Graduados de la Facultad de Ciencias Médicas de la Universidad Nacional de Buenos Aires, Paraguay 2155, para el Curso Completo de Gastroenterología que dictará en el Hospital Nacional de Gastroenterología "DR. BONORINO UDAONDO", el Docente autorizado de Cirugía, Dr. Marcos Maur, con la colaboración de los siguientes Especialistas del mencionado Establecimiento: Dres. Manuel M. Ramos Mejía, Adolfo M. Rey, Victorino D' Alotto, Manuel Lemos García, Adolfo Schapira, Alfonso Fraise, Solomón Krigpún, Julio C. Rojas, Pedro Scorza, Leonardo Braier, Jorge Caffarello, Horacio Capizzano, Aldo Copello, Erman Crosetti Emilio Chattás, Fernando Galindo, Atilio Iorio, Ricardo A. Sabagh, Isaías Schor, Ramón Pando, Raúl Rodríguez, Alberto Apud, Ricardo de Elizalde, León Kesner, Antonio Musi, Gustavo A. Schickendantz., Ricardo Vivone y Luciano Bombaci. Actuará de Encargado Suplente del Curso el Docente autorizado de Cirugía Dr. Pedro Cotella.

El Curso tendrá una duración de 8 meses, desde el 4 de abril al 5 de diciembre. Los médicos inscriptos deberán concurrir todos los días hábiles de 7:30 a 12 horas, pudiendo inscribirse egresados de hasta cinco años. Para médicos residentes en otros países, no hay límite de antigüedad pero deben traer en el momento de inscripción, el título de médico o bien copia autenticada del mismo.

Está Previsto el Siguiente Programa Teórico:

Clases Magistrales los días lunes y viernes a las 11 horas, sobre distintos aspectos de Fisiopatología Gastroenterológica abarcando toda la Patología Digestiva. Aprendizaje de los distintos medios complementarios de diagnóstico: Radiología, Endoscopía, Laboratorio, Clases de Dietología vinculadas a Patología Digestiva, Clases de Medicina Psicosomática en relación con la Gastroenterología

Ateneos de: Radiología, Anatomía Patológica, Clínico-Quirúrgico y Bibliográfico así como un cursillo de Cirugía Experimental. Para las Clases Prácticas, que también tendrán desarrollo todos los días de 7:30 a 11 horas, se constituirán seis comisiones que rotarán por los siguientes Servicios; Clínica, Nutrición, Laboratorio de Investigaciones, Radiología, Endoscopía, y Proctología.

Los inscritos cirujanos, además de realizar instrucción en los Servicios indicados en el párrafo precedente, realizarán ejercicios de Cirugía Experimental y los tres últimos meses se adscribirán al Servicio de Cirugía del Establecimiento, donde actuarán en el mismo plano que los médicos becarios con que cuenta el Hospital.

El Departamento de Graduados de la Facultad otorgará certificación a los inscritos que hayan cumplido con el 80% de las actividades previstas. Para información complementaria dirigir carta al Director del Curso, Avenida Caseros 2061, Buenos Aires, Argentina, o bien personalmente a la Biblioteca del Hospital, tercer piso, teléfono No. 27-4641.

Agosto 20-25, 1966 *Noveno Congreso Internacional de Enfermedades del Tórax.*

The Board of Trustees of the Pan-Pacific Surgical Association announces the dates of the Tenth Congress in Honolulu and the Second Mobile Educational Seminars which travels to countries bordering the Pacific basin.

Part I, the Honolulu portion of the Congress, will convene at the Princess Kaiulani Hotel on September 20, 1966, and continue through September 28.

Part II and III will depart Hawaii on September 28 and travel to Japan and Hong Kong with Part II returning to San Francisco on October 10, in time for the opening of the American College of Surgeons, and Part III continuing on to the Philippines, Thailand, India, Singapore, Australia and New Zealand, returning to Hawaii on November 1,1966.

The Tenth Congress offers an extensive scientific program presented by more than 450 leading surgeons from the United States and 22 other countries in 12 different specialties: Colon and Anorectal Surgery, General Surgery, Neurosurgery, Obstetrics and Gynecology, Ophthalmology, Otolaryngology, Orthopedics, Plastic Surgery, Thoracic-Cardiovascular Surgery, Urology, Anesthesiology and Radiology. All physicians and surgeons are invited to attend these meetings.

In this space age, diseases are no longer confined to geographical boundaries and it has become essential for the medical profession everywhere, to share its scientific knowledge and efforts. Therefore, Pan-Pacific with its Mobile Seminars, is expanding its activities in teaching, education and dissemination of knowledge to doctors living in the Pacific rim countries who are unable to participate in the Honolulu portion of the Scientific Congresses, in exchange for further education and skill in the diseases unique to the Pacific areas. The Pan-Pacific Surgical Association believes, through the vehicle or medium of medicine and surgery, that our greatest contribution to peace and harmony among all men of all nations can be realized.

For further information, please write: Pan-Pacific Surgical Association, Room 236, Alexander Young Building, Honolulu, Hawaii 96813.

Oct. 23-29, 1966 IX International Cancer Congress, Tokyo, Japan. A charter flight and several group flights are contemplated, thus substantially reducing the cost of transportation. Members of the immediate family of congress participants will be eligible. Anyone interested should communicate with Hirsch Marks, M.D., 435 East 57th Street, New York 22, N.Y.

Instrucciones para los Autores:

El Boletín acepta para su publicación artículos relativos a medicina y cirugía y las ciencias afines. Igualmente acepta artículos especiales y correspondencia que pudiera ser de interés general para la profesión médica.

El artículo, si se aceptara, será con la condición de que se publicará únicamente en esta revista.

Para facilitar la labor de revisión de la Junta Editora y del impresor, se requiere de los autores que sigan las siguientes instrucciones:

a) Los trabajos deberán estar escritos a máquina a doble espacio y por un solo lado de cada página, en duplicado y con amplio margen.

b) En página separada debe incluirse lo siguiente: título (no excediendo de 80 letras y espacios), nombre del autor (es), institución y dirección postal del autor.

c) Artículos referentes a resultados de estudios clínicos o investigaciones de laboratorio deben organizarse bajo los siguientes encabezamientos: (1) introducción, (2) material y métodos, (3) resultados, (4) discusión, (5) resumen (en español e inglés), y (6) referencias.

d) Artículos referentes a estudios de casos aislados deben organizarse en la siguiente forma: (1) introducción, (2) observaciones del caso, (3) discusión, (4) resumen (en español e inglés), (5) referencias.

e) Las tablas, notas al calce y leyendas deben aparecer en hojas separadas.

f) Si un artículo ha sido leído en alguna reunión o congreso, así debe hacerse constar como una nota al calce.

g) Deben usarse los nombres genéricos de los medicamentos. Podrán usarse también los nombres comerciales, entre paréntesis, si así se desea.

h) Se usará con preferencia el sistema métrico de pesos y medidas.

i) Las fotografías y microfotografías se someterán como copias en papel de lustre sin montar. Los dibujos y gráficas deben prepararse a tinta negra y en papel blanco. Todas las ilustraciones deben estar numeradas (números arábigos) e indicar la parte superior de las mismas. Debe escribirse una leyenda para cada ilustración.

j) Las referencias deben ser numeradas sucesivamente de acuerdo con su aparición en el texto. Los siguientes ejemplos pueden servir de modelo:

6. *Koppisch, E.* Pathology of arteriosclerosis. Bol. Asoc. Med. P. Rico 46: 505, 1954. (artículo de revista).
4. *Wintrobe, M. M.* Clinical Hematology, 3rd Ed. Lea and Febiger, Philadelphia, 1952, p. 67. (libro).

Deben usarse solamente las abreviaturas indicadas en el Cumulative Index Medicus que publica la Asociación Médica Americana.

Instructions to Authors:

The Boletín will accept for publication contributions relating to the various areas of medicine surgery and allied medical sciences. Special articles and correspondence on subjects of general interest to physicians will also be accepted. All material is accepted with the understanding that it is to be published solely in this journal.

In order to facilitate review of the article by the Editorial Board and the work of the printer, the authors must conform with the following instructions:

a) The entire manuscript, including legends and references, should be typewritten double-spaced in duplicate with ample margins.

b) A separate title page should include the following: title (not to exceed 80 characters and spaces), author's name (s); institution, and author's mailing address.

c) Articles reporting the results of clinical studies or laboratory investigation should be

organized under the following headings: (1) introduction, (2) material and methods, (3) results, (4) discussion, (5) summary in English and Spanish, (6) references.

d) Case reports will include (1) introduction, (2) description of the case, (3) discussion, (4) summary in English and Spanish, (5) references.

e) Tables, footnotes and legends to figures should appear in separate sheets.

f) If the paper has been presented at a meeting, the place and date should be stated as a footnote.

g) Generic names of drugs should be used. Trade names may also be given in parenthesis, if desired.

h) Metric units of measurement should be used preferentially.

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6. *Koppisch, E.* Pathology of arteriosclerosis. Bol. Asoc. Med. P. Rico 46: 505, 1954. (for journal articles).
4. *Wintrobe, M. M.* Clinical Hematology, 3rd Ed. Lea and Febiger, Philadelphia, 1952, p. 67, (for books).

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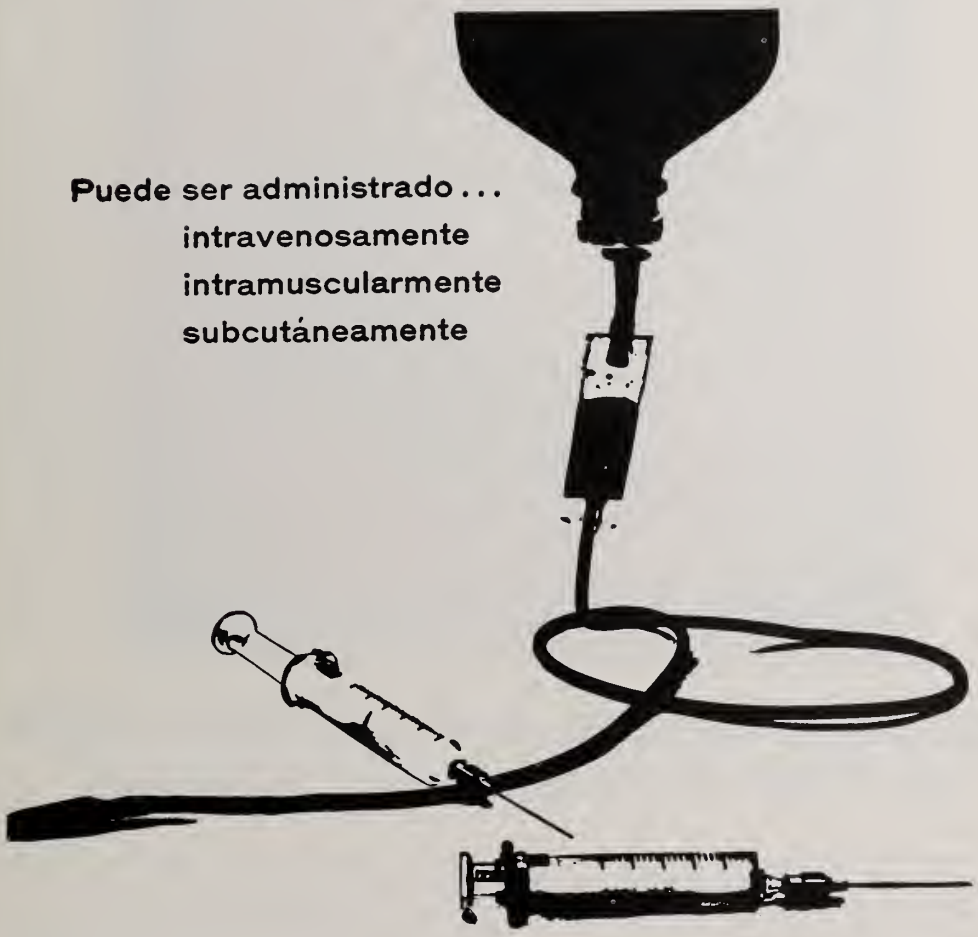
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1. Cirelli, M.G.: Delaware M. J. *34:*159 (junio) 1962. 2. Martin, G. J.; Ehrenreich, J.; y Asbell, N.: Exper. Med. & Surg. *20:*227 (sept.) 1962.

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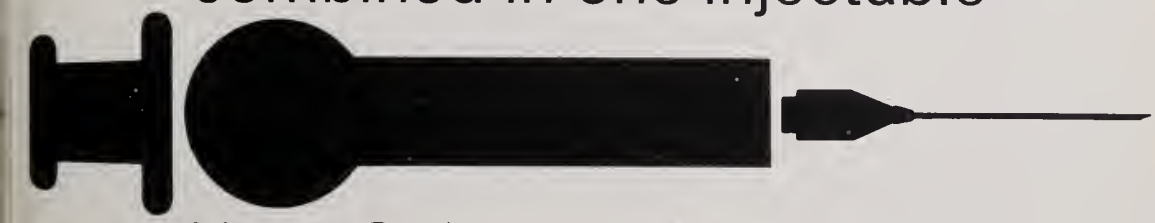
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Martin, *et al.*, quienes examinaron 58 casos de relajaciones, esguinces y dislocaciones, informan que la respuesta a ANANASE fue superior a la terapia corriente en 82,8% de los casos.[2]

El empleo de ANANASE como terapia coadyuvante en el próximo caso de dislocación, fractura o traumatismo grave de los tejidos blandos que trate le probará que puede disminuir el dolor y la hinchazón y reducir el tiempo y el costo de la convalecencia. Para obtener los mejores resultados administre ANANASE *lo antes posible* y en *dosis máximas.*

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1. Cirelli, M. G.: Medical Times 92:919 (sept.) 1964. 2. Martin, G. J.; Ehrenreich, J.; y Asbell, N.: Exp. Med. & Surg. 20:227 (sept.) 1962.

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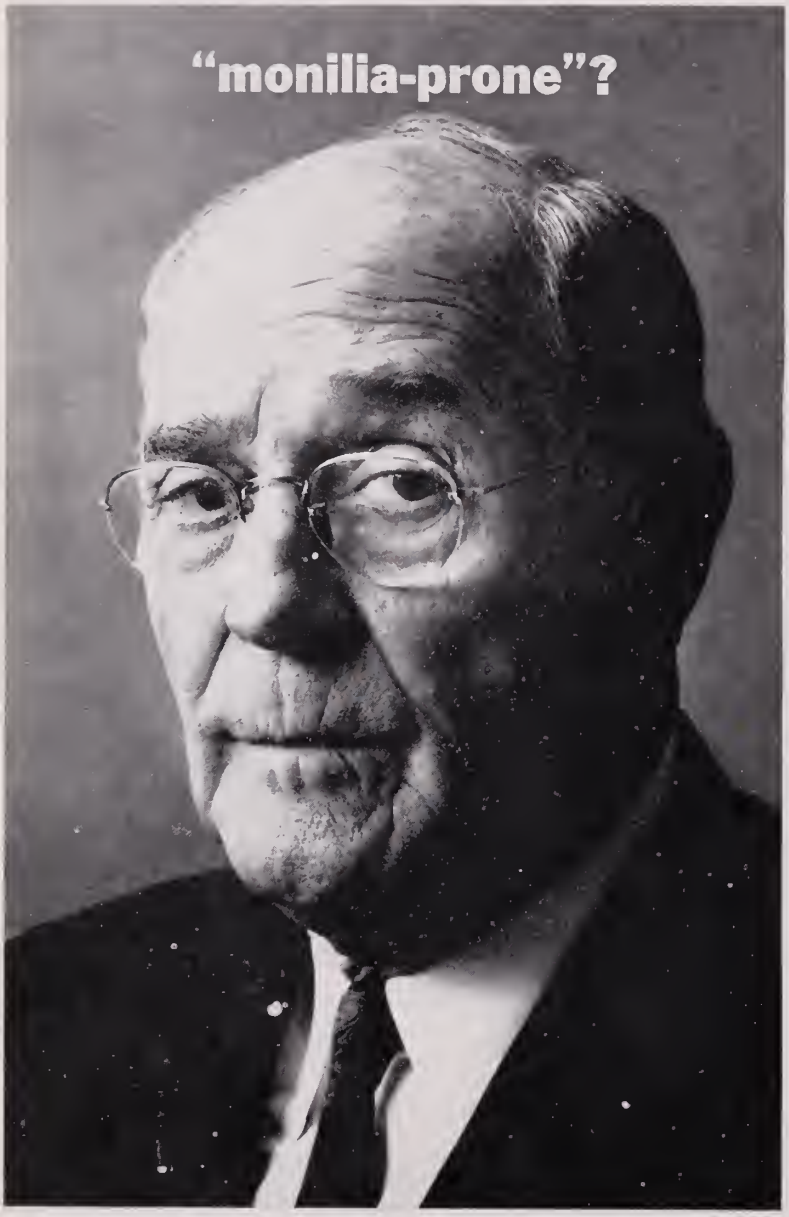
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AUTOLOGOUS BLOOD TRANSFUSION IN CARDIOVASCULAR SURGERY

Leo Cuello, M.S., M.D.
Enrique Vázquez, M.D.
Víctor Pérez, B.S., M.T.
F.L. Raffucci, M.S., M.D., F.A.C.S.

The scarcity of blood and the danger of infectious hepatitis and transfusion reactions have opened the search for blood substitutes or methods to avoid or reduce the use of homologous blood, pooled plasma or substitutes.

The use of an autologous blood transfusion has been reported sporadically in the medical literature. Autotransfusion can be used either during emergency for lifesaving procedures or during an elective operation. In 1818, an obstetrician named John Blundell (1) utilized vaginal blood in ten patients with severe post partum hemorrhage with a mortality of 50%. About 1860, Braxton Hicks (1) tried autotransfusion using ammonium sulfate as an anticoagulant, but abandoned it because of the latter's toxicity. Volkmann (2) in discussing disarticulation at the hip joint suggested the possibility of utilizing the blood lost during the operation and returning it to the patient through the divided femoral vein.

This work was supported in part by: U.S.P.H.S. AM-4158 Liver Injury and Regeneration, Grant FR-63-03, Division of General Medical Sciences, National Institutes of Health, by the Jerrold Von Wedel Foundation and by Chemicals Incorporated, San Juan, Puerto Rico.

Presented at the 18th Annual Meeting of the American Association of Blood Banks, Bal Harbour, Florida, September 17, 1965.

In 1883, Halstead (2) reported on the use of "refusion" in treatment of carbon monoxide poisoning. His patients were bled and the defibrinated blood was reinfused. In 1931, Lincoln Brown and Martin Warren Debenham (3) reported a case in which blood obtained from a hemothorax secondary to a stab wound was used as an autotransfusion. In 1956, Eteuati Leiato (1), a young Samoan medical practitioner on the island of Manua, treated a 28 year old patient who had profuse vaginal bleeding secondary to placenta previa with her own blood. He collected the blood in a sterile obstetrical basin, diluted it with saline and gave it immediately to the patient. She received 1000-1500cc of her own blood thus obtained and delivered a normal viable baby. No postpartum complications attended the use of this blood. The use of autotransfusion in elective surgical operations was first reported by Grant (4) in 1921. The patient had a cerebellar tumor and a rare type of blood. A phlebotomy was performed 24 hours prior to the operation and the patient was autotransfused following the operation without untoward effects. Four days after the operation the red cell count, hemoglobin and blood pressure were normal. In 1962, Milles and his group (5) reported their experience with autotransfusion. Fifty-three patients underwent different operations

among which were: pulmonary lobectomy, cholecystectomy and colon resection. In 1963, the same authors published (6) another report on the use of autotransfusion in 113 patients and it was found that the reticulocyte count increased only slightly and there was no significant changes in blood pressure, bleeding and clotting time or platelet count. The level of hemoglobin and hematocrit decreased after venesection, but compensation insofar as total blood volume is concerned occurred. In January 1964, García and Zamora (7) published on the use of autotransfusion in elective thoracic operations. Autotransfusion was used on ten patients; among the operations performed were pulmonary lobectomy, excision of mediastinal tumors and one subclavio-pulmonary anastomosis (Blalock-Taussig operation).

Materials and Methods

This study consists of 51 patients admitted to the Surgical Department (Thoracic and Cardiovascular Service) of the University Hospital during the past two years. There were two cyanotic patients in the whole group. Their ages ranged from four years to 76 years with a mean age of 36.5 years. Their weigth ranged from 40 pounds to 174 pounds with an average of 122 pounds. The operation was planned from one to 15 days after the first phlebotomy. On a group of patients phlebotomy was peformed from one to five days prior surgery. In those patients on whom several preoperative phlebotomies were performed, an interval of five to six days between phlebotomies was allowed. The usual bleeding volume was 500ml. The total amount of drawn blood per patient varied from 200ml to 2000ml. Blood was collected using the routine blood bank technique.

Eleven patients underwent correction of their cardiovascular defects on cardiopulmonary by-pass using the De Wall-Lillehei bubble oxygenator. Hemodilution (8) with 10% Low Molecular Weight Dextron* (LMWD) was used on all patients. The priming volume was 20ml of LMWD/kilogram of body weight. Tables I and II demonstrate: (1) the number of patients, (2) their ages, (3) their disease, (4) the volume of autodonated blood, (5) the amount and source (autologous and/or homologous) of the blood used during and after completion of the surgical procedure.

Hematocrit and hemoglobin determinations were done on all patients before and after each phlebotomy (two to 12 hours post-phlebotomy); as well as in the immediate postoperative period and upon discharge. Blood volume determinations with I^{131}-labeled albumin were performed in ten patients. Daily determinations of reticulocytes were done pre and postoperatively in seven of these ten patients. All our patients received iron hydrogenated dextran complex** intramuscularly to insure optimal absorption. The amount given was calculated by the standard formulas:

$$0.3 \times \text{Weight in pounds} \times \frac{(100 - \%\ \text{of patient's hemoglobin})}{50} = \text{cc of iron hydrogenated dextran complex}$$

The amount calculated provides an excess of 30-40% over the necessary to reestablish the iron reserves of the organism The total dose was divided in ten doses and administered daily or every other day. The administration of iron was continued postoperatively. Upon discharge the patients were placed on oral iron therapy of three to four weeks duration.

Results

A total of 50 operations were performed on these patients; two patients refused surgery and one was operated upon twice thus a total of 75 phlebotomies were performed in 51 patients. Except for two patients who had 350ml and 200ml of blood drawn the

* *Rheomacrodex, Pharmacia, Uppsala, Sweden.*

** *Iron Hydex 50. Each ml contains 50mgs of iron hydroxide, 15-20% of hydrogenated dextran and 0.5% of phenol. Kindly supplied by Chemicals, Inc. San Juan, Puerto Rico.*

other phlebotomies were of 500ml. Thirty patients underwent a single phlebotomy; 15 patients, two phlebotomies; three patients, three phlebotomies (1500ml); and one patient underwent four phlebotomies (2000 ml).

During the actual surgical procedure 93.8 units of blood (500ml/unit) were used of which 56.5 units were autologous and 37.3 homologous. Post-operatively 4.5 units of autologous blood and 27 units of homologous blood were transfused. A total of 61 units of autologous blood were administered versus 64.3 units of homologous blood of which 56.5 units were on cases of open heart surgery.

All patients except one had hematocrit levels above 35mm% before the first phlebotomy (See Figs. 7 and 8). The mean value of the pre-donation hematocrit was 41.6%; before surgery was 37.5% and in the immediate post-operative period was 38%.Only three patients had a hematocrit below 30% after surgery; two of which were operated on cardiopulmonary by-pass with hemodilution. In those patients on whom blood volume determinations were done, a compensatory increase in plasma volume and a small decrease in red blood cell mass was observed. The reticulocyte count increased up to two or three per cent, but it never exceeded five per cent. (See Fig. 6) Of a total of 50 operations 30 were thoracotomies and 15 were done with autologous blood exclusively. (Table I) These 15 patients underwent the following operations: correction of a patent ductus arteriosus (17, 18, 31 and 33 years), resection of a coarctation of the aorta (15, 23, 25 and 32 years), closure of an atrial septal defect (25 years), a Blalock-Taussig shunt on a tetralogy of Fallot (35 years), a valve replacement on an aortic stenosis and insufficiency (14 years), lobectomy for saccular bronchiectasis (20 years), resection of a mediastinal parathyroid adenoma (34 years) and an exploratory mediastinotomy (27 years). A four year old patient with tetralogy of Fallot required no blood replacement. Figure 7 shows the amount of autodonated blood and the changes in hematocrit. The remaining 14 patients underwent thoracotomies and received variable amounts of homologous blood in addition to the autologous transfusions. (See Table I-B and Fig. 2.) Nineteen miscellaneous operations were performed, 11 of which were done with autologous blood only (Table II - A and Figs. 3 and 8); three with autologous and homologous blood (Fig. 4) and five required no blood replacement. Figure 5 illustrates this latter group.

There were five deaths in the whole series. They occurred among the group of patients who underwent open heart surgery and were distributed as follows: 1) one patient with a large atrial septal defect with anomalous pulmonary venous drainage (36 years) and pulmonary hypertension, (2) two patients who underwent mitral valve replacement with the Starr-Edwards ball valve prosthesis (42, 22 years), 3) one patient with congenital valvular and diffuse subvalvular aortic stenosis and insufficiency who underwent an aortic valve replacement with a Magovern-Cromie ball valve prosthesis (14 years), 4) one patient with a syphilitic aneurysm of the ascending aorta (61 years).

Discussion

The effect of blood donation is very well documented in the medical literature (9, 10, 11, 12). Cadham (10) studied the effects

TABLE I: THORACOTOMIES

	Diagnosis	No. of Patients	Age	Augologous Blood Units	Homologous Blood Units
I. Thoracotomies					
A. Autologous Blood	1—Patent Ductus Arteriosus	4	17, 18, 31, 33	2-1-2-2	
	2—Coarctation of Aorta	4	15, 23, 25, 32	1-1-2-2	
	3—Atrial Septal Defect	1	25	1	
	4—Tetralogy of Fallot	1	35	3	
	5—Aortic Insufficiency	1	14	2	
	6—Complete Heart Block (Implantable Pacemaker)	1	49	1	
	7—Hyperparathyroidism	1	34	1	
	8—Saccular Bronchiectasis	1	20	1	
	9—Myocarditis	1	27	2	
		Total 15	Average Age 26.5	Total 24	
B. Autologous and Homologous Blood	1—Mitral Stenosis and/or Insufficiency (Valve Replacement)	6	22, 23, 33, 39, 42, 44	1-1-2-1-2 3	4-9-4-12½ 5-1
	2—Mitral Stenosis (Commissurotomy)	2	15, 36	1-2	2-3½
	3—Atrial Septal Defect (Secundum) with Cleft Mitral Valve	1	22	1	4
	4—Atrial Septal Defect	1	36	2	2
	5—Coarctation of Aorta	1	18	1	1
	6—Pulmonic Stenosis	1	18	1	1 (250cc packed cells)
	7—Ascending Aorta Aneurysm	1	61	1	9
	8—Subclavian Steal	1	50	2	1
	Total	14	Average Age 32.6	Total 21	Total 58½
C. Autologous Blood Saved	1—Tetralogy of Fallot	1	4	1 (200cc)	
	2—Mitral Insufficiency	1*	17	3	
	3—Mitral and Aortic Insufficiency	1*	35	4	
	Total	3	Average Age 18.7	Total 8	

*Not operated upon.

TABLE II: OTHER OPERATIONS

	Diagnosis	No. of Patients	Age	Autologous Blood Units	Homologous Blood Units
II. Miscellaneous					
A. Autologous Blood	1—Portal Hypertension (Porto Caval Shunt)	3	44, 60, 68	1-1-2	
	2—Arteriosclerosis Obliterans (Bilateral Sympathectomy)	2	47, 76	1-1	
	3—Hiatal Hernia	1	65	1	
	4—Abdominal Aorta Aneurysm	1	42	2	
	5—Pulmonary Embolism (Inferior Vena Cava Ligation)	1	43	1	
	6—Temporal A-V Fistula	1	15	2	
	7—Femoral Artery Occlusion Femoral By-pass)	1	51	1	
	8—Femoro-Popliteal Endarterectomy	1	52	1	
		Total 11	Average Age 51.2	Total 14	
B. Autologous and Homologous Blood	1—Portal Hypertension (Porto Caval Shunt)	1	55	1	1
	2—Femoral Occlusion (Aorto-Femoral By-pass)	1	47	1	2
	3—Bilateral Renal Artery Stenosis (Aorta-Right Renal Graft)	1	24	1	1
		Total 3	Average Age 41.3	Total 3	Total 4
C. Autologous Blood Saved	1—Arteriosclerosis Obliterans (Unilateral Sympathectomy)	2	35, 57	1-1	
	2—Arteriosclerosis Obliterans (Bilateral Sympathectomy)	1	65	1 (350cc)	
	3—Hiatal Hernia	1	59	1	
	4—Pulmonary Embolism (Inferior Vena Cava Ligation)	1	42	1	
		Total 5	Average Age 51.6	Total 5	

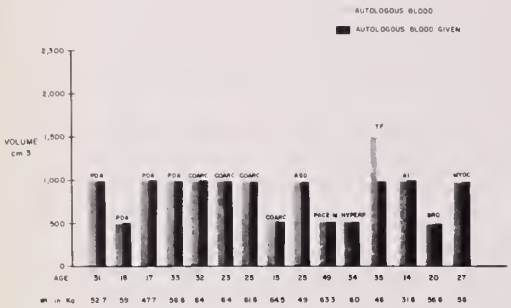


Fig. 1: Volume of blood tansfused—thoracotomies with autologous blood only.

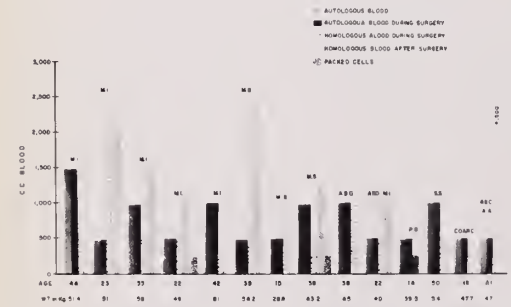


Fig. 2: Volume of blood transfused—thoracotomies with autologous and homologous blood.

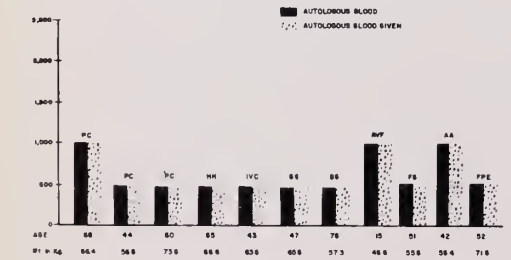


Fig. 3: Volume of autologous blood transfused—miscellaneous operations.

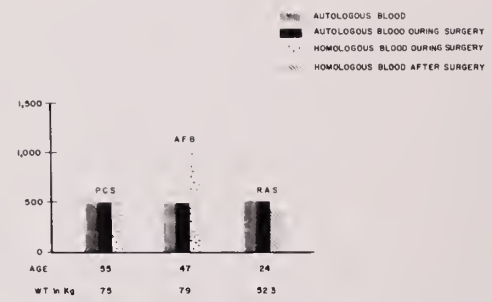


Fig. 4: Volume of blood transfused—miscellaneous operations with autologous and homologous blood.

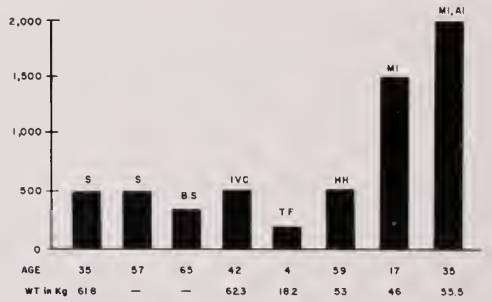


Fig. 5: Volume of autologous blood saved.

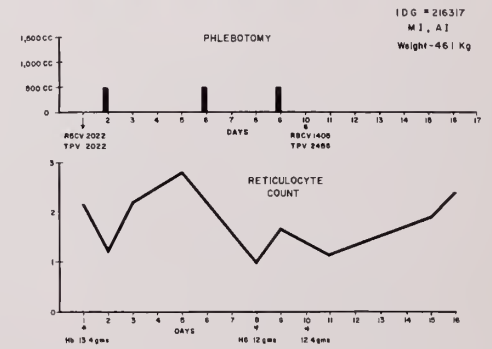


Fig. 6: Reticulocyte and homoglobin levels following phlebotomies.

of small and large donations and concluded that small donations are tolerated better.

In 1941, Ebert (13) demonstrated that the plasma volume began to increase immediately after hemorrhage and continued to increase for the next 48 to 72 hours. During the first two hours, the plasma volume was increased by protein-poor fluid, so that

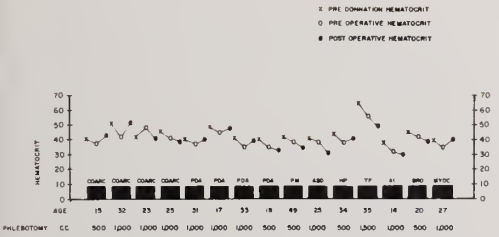


Fig. 7: Hematocrit values before and after thoracotomy with autologous blood transfusions.

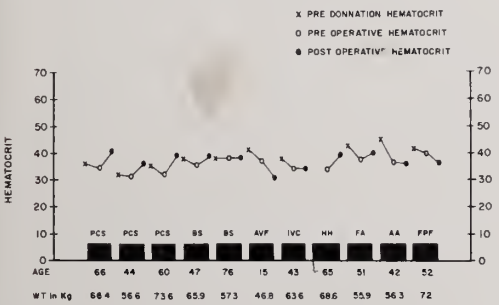


Fig. 8: Hematocrit values before and after miscellaneous operations with autologous blood transfusions.

the serum protein concentration decreased. Thereafter, fluid and protein was added to the intravascular compartment thus resulting on an increase on the total circulating protein. The loss of blood acted as a physiologic stimulus for the production of normal protein, and the addition of new protein did not change the proportion of albumin and the various globulin fractions.

The rate of blood regeneration following phlebotomy is dependent chiefly on available body stores of iron (14). In patients with excessive tissue iron including those with hemochromatosis, blood production continues at an accelerated rate, and weekly phlebotomies could be continued for several months without the development of anemia (9). While in those individuals with depleted iron stores, hematopoiesis is severely affected. Furthermore, Hahn (15), Finch (16) and Bothwell (17) have stated that following acute phlebotomy there is a four to five day delay before iron absorption is increased. Recently, Crosby (18) and co-workers have confirmed this finding. Thus the use of intramuscular iron provides adequate iron levels rapidly avoiding the lag period of intestinal iron absorption.

Erythropoiesis is a continuous physiological process that may be altered in opposite directions. The hormone that regulates this process (19) "erythropoietin" seems to be totally produced in the kidneys and its secretion depends mainly on the arterial oxygen tension (PO^2) A decrease in hemoglobin level will result in an increased erythropoietin secretion and consequently in an accelerated erythropoiesis. This series of reactions will occur after blood loss. Among the many factors (19) which depress erythropoiesis overtransfusion is one of them.

All this evidence plus the clinical work of Milles (5) and others (6,7) led us to use autologous blood in patients with cardiovascular lesions. Since many of these operations require more than one unit of blood, it seemed practical and beneficial to the patient to obtain an early stimulation of their erythropoiesis and to abolish or minimize the depressive action of homologous blood to erythropoiesis.

The experience and the confidence gained in this method has increased the number of phlebotomies to two and three in our last cases.

The five deaths were not attributable to the phlebotomy itself, but to the severity of the cardiovascular lesions.

The most important advantages obtained with the use of autotransfusion are the fol-

lowing: the prevention of transfusion reactions, the prevention of serum hepatitis and other infections, the availability of rare blood groups, an early reticulocytosis and accelerated erythropoiesis and a ready source of safe blood even in those places where it is readily available.

Summary

Fifty-one patients admitted to our Cardiovascular Service were bled a few days prior to surgery. Of these, 30 underwent thoracotomies of which 15 were performed using their own blood only, the remaining requiring small amounts of bank blood. Sixty per cent of the blood used during surgery was autologous blood. No deleterious effects were observed among these patients with cardiovascular diseases. The advantages enumerated and the proven safety merit the continued use of this procedure in practically all types of surgical procedures.

Resumen

A 51 pacientes admitidos al Departamento de Cirugía (Servicio Cardiovascular) se les practicó una o más flebotomías. De este grupo 30 fueron sometidos a toracotomías: en 15 se usó sangre autóloga solamente y en los restantes se utilizaron pequeñas cantidades de sangre homóloga. Sesenta por ciento de la sangre usada durante el procedimiento quirúrgico fue sangre autóloga. No se observó ningún efecto adverso en estos pacientes con enfermedades cardiovasculares. Las ventajas enumeradas y la seguridad del procedimiento ameritan su uso en cualquier tipo de intervención quirúrgica.

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ALBUMIN LOSS IN EXPERIMENTAL GASTRITIS

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Sergio Irrizarry, M.D.
Myrna I. Rivera, B.S.

Previous studies of German authors, have documented the presence of serum albumin in abnormal amounts in the gastric juice of infectious and serous gastritis. Katsch (1) demonstrated significant amounts of albumin in infectious and serous types of gastritis. This same author and Baltzer (2) had developed a method based on the turbidity produced by the action of sulfosalicylic acid in albuminous fluids.

Citrin (3) described the syndrome of "hypercatabolic hypoproteinemia" secondary to the great loss of albumin in cases with giant hypertrophic gastritis. Butz (4) confirmed this finding. Norpoth, Surman and Cloesges (5) demonstrated in the gastric juice the presence of albumin of "inflammatory" origin by means of paper electrophoresis. Keinkel, Preisser and Henning (6) showed that patients suffering from atrophic gastritis have low levels of serum albumin. Glass and Ishimori (7) demonstrated on paper electrophoresis that the gastric juice of patients with superficial gastritis and "hyperacid" gastritis contain the degradation products of serum albumin.

From the schools of Pharmacy and Medicine and the Clinical Applications Division, Nuclear Center, University of Puerto Rico, San Juan, P.R.

Zeneida Frias and Elba M.V. de Rodríguez, participated in this study.

Material and Methods

This work has been done on mongrel dogs weighing approximately 30 pounds. The animals were prepared two days prior to the experiment with the administration of 0.5ml Lugol's solution two times daily for saturation of the thyroid.

Three dogs served as controls. Each animal received an intravenous injection of 26 uc of I^{131} albumin (RISA) diluted with carrier albumin; the radioactive solution containing specific activity of 2.6 uc/ml. Blood samples for counting were obtained 10 minutes after injection to determine the initial level of activity in the plasma.

The initial level of activity at 10 minutes post-injection was used for reference for other samples to be obtained later. Blood was again sampled for radioactive assay at frequent intervals during the first 8-10 days. On the fourth day after the injection of RISA, the gastric juice was examined. The gastric juice was obtained under a standardized procedure:

a - Histalog® (25 milligrams) injected, animal fasting.
b - Nembutal anesthesia, intravenous induction 25 minutes after Histalog®.
c - Intubation of stomach with animal in left decubitus position, evacuation of gastric juice effected and this sample discarded.
d - Then for the next 30 minutes the gastric juice collected by continous aspiration is measured in toto and sent to the laboratory for radioactive analysis.

The same procedure was used in the following groups of animals:

I - Two dogs received 2ml Creosote 2 + ml Diol

6 days weekly for 64 days. These animals developed the so-called serous gastritis with congestion, capillary dilatation, edema and little cellular reaction. Following the induction of these changes, the animals received 26 μc RISA intravenously and examined according to the procedure just outlined above.

II - Two dogs were treated with an aqueous solution of cincophen (atophan) by gastric tube twice weekly. With this method (8) an ulcerative gastritis of the body and antrum of the stomach is produced characterized by the presence of multiple superficial erosions the majority being one millimeter in size. The basement membrane is edematous and moderately infiltrated with neutrophiles (Figs. 1 and 2). The procedure with RISA was started on the first day of the next week, under the same conditions as with the other tests.

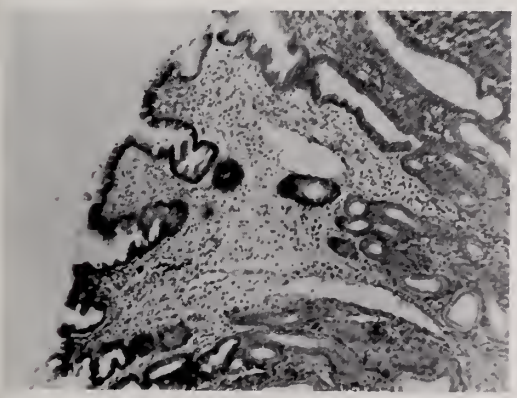


Fig. 1: Atophan induced gastritis in dog. Glandular dilatation, edema of the lamina propria, infiltration.

III - Three dogs were treated with 3 milliliters of a 0.5% croton oil alcohol ether solution instilled into the upper part of the stomach thru a ureteral catheter inserted inside a gastric tube. Twenty-six μc RISA was administered to this group of animals as already described. These dogs developed a papillomatous type of gastritis * (Figs. 3,4 and 5). All the animals of the three groups were sacrificed at the end of the experiment and the stomach examined histopathologically.

*This gastritis will be described in a separate work to be published by Drs. Rodríguez Olleros and Dr. L. Galindo.

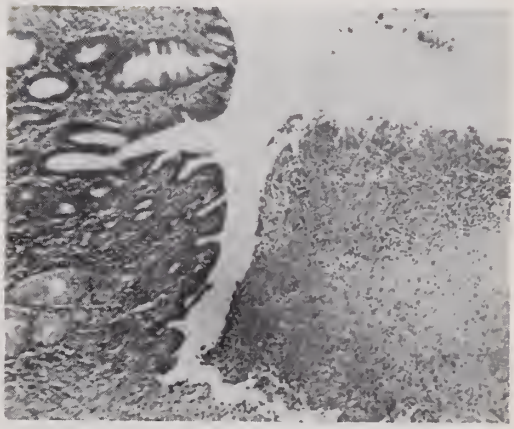


Fig. 2: Atophan induced gastritis in dog: superficial ulceration.

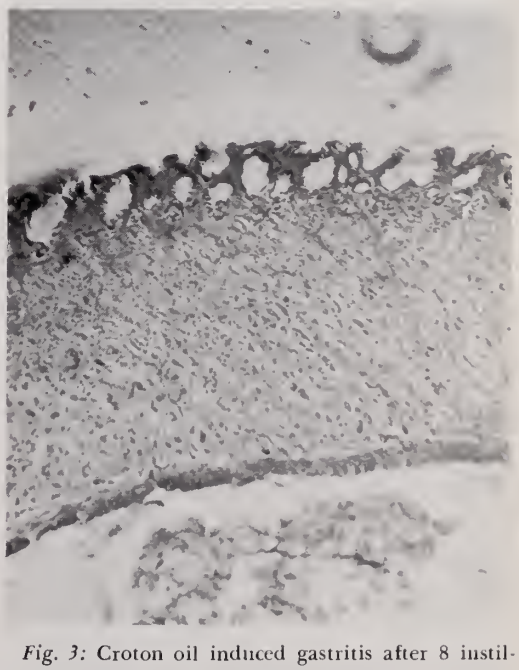


Fig. 3: Croton oil induced gastritis after 8 instillations. Parallel structure of glands lost, early dilatation of superficial gland.

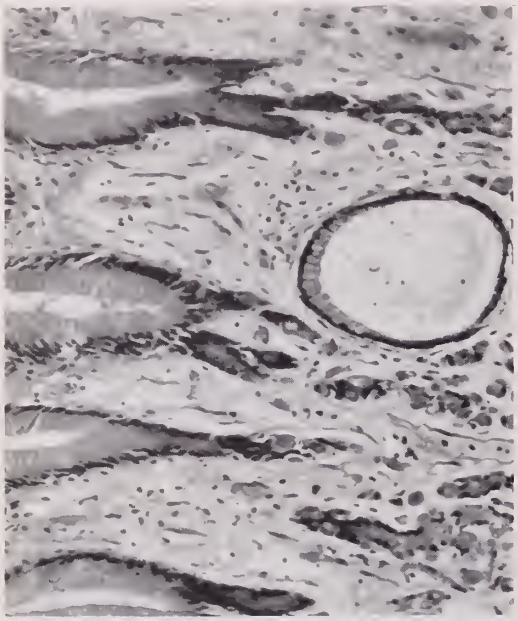


Fig. 4: Croton oil induced papillomatous gastritis. After 8 instillations. Cyst, marked edema, round cell infiltration and scant eosonophiles.

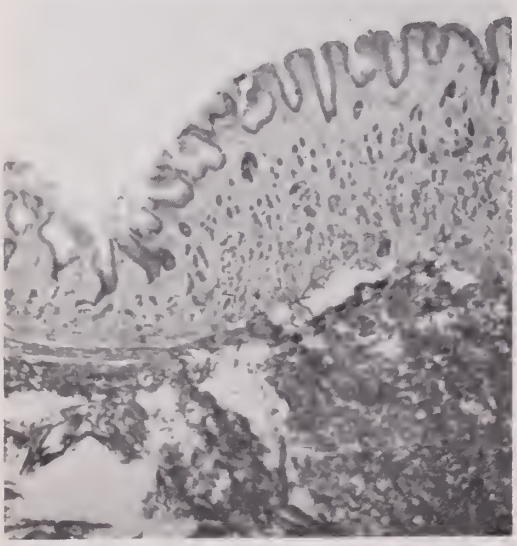


Fig. 5: Croton oil induced papillomatous gastritis. Contrast between hyperplastick area and the narrow region with edema of the gastric wall.

Results

Ten animals comprised the entire group under study: 3 as controls and seven experimental. The disappearance half time of albumin I^{131} in blood and its level of activity in the gastric juice were determined before and after the experimental induction of gastritis in animals 1, 2 and 3 which acted as controls for themselves and for the remaining animals in which measurements after the experiment were done only (Table I).

To assess the reliability of the I^{131} tag for the decay curves of albumin in the blood, an *in vitro* curve was obtained of a solution of albumin and the measurements were obtained for the whole solution, and the trichloroacetic acid-washed precipitate. In a period of 10 days it was demonstrated that the inorganic fraction of I^{131} is negligible as compared to the organic fraction. A similar analysis of radioactivity was carried out on

TABLE I: PARTITION (%) FREE IODINE I^{131} OF TOTAL RADIOACTIVITY IN BLOOD AT TIME OF GASTRIC JUICE SAMPLING

Animal	Pre	Post
1.	2.7	5.1
2.	4.2	7.9
3.	6.7	5.7
6.	—	8.8
7.	—	5.4
4.	—	0
5.	—	2.3

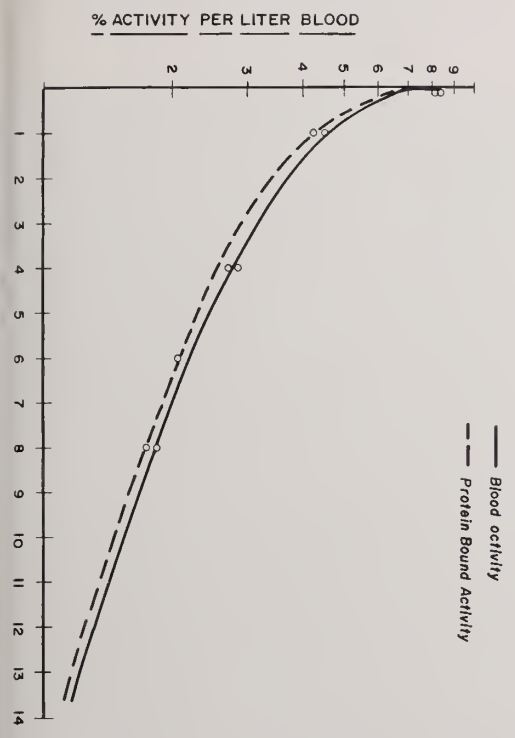


Fig. 6: In Vivo partition between free and protein bound I-131

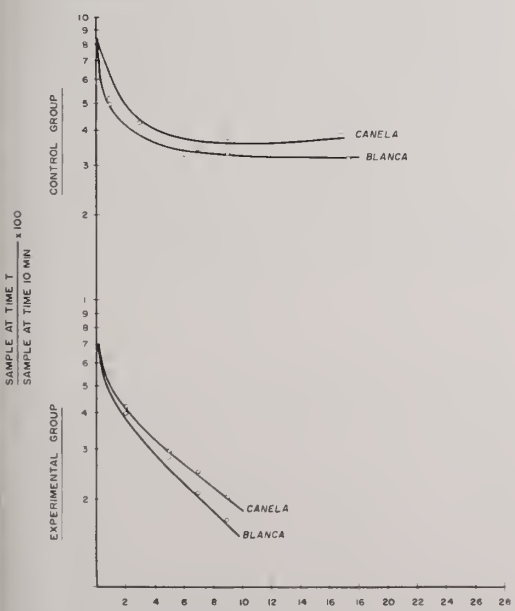


Fig. 7: T ½ albumen I-131

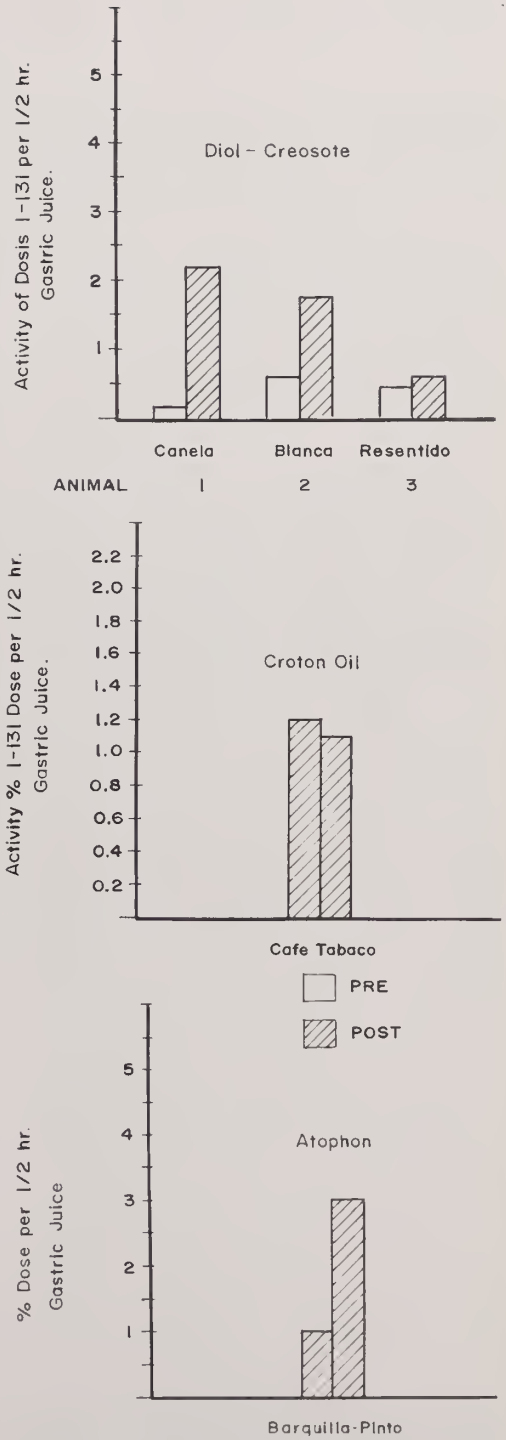


Fig. 8: Transudation Albumen I-131 gastritic juice

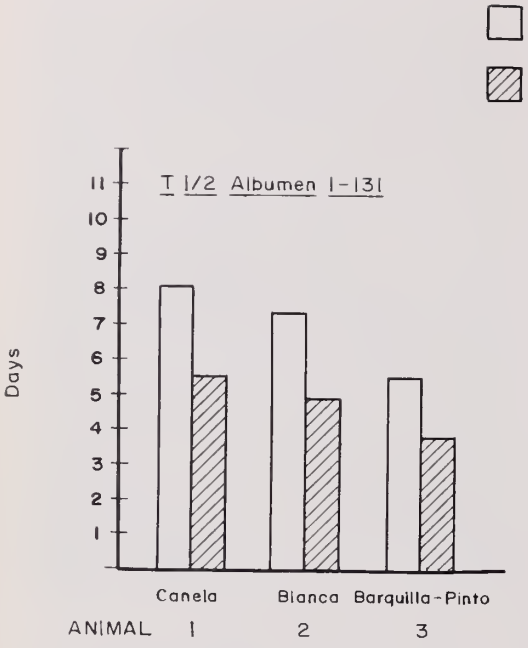


Fig. 9: Gastritis diol-creosota and croton oil

all blood samples and the proportion of free iodine in plasma compared to that bound to albumin was determined on the same day the gastric juice was sampled. The proportion of free I^{131} to whole blood activity averaged 4.9% on the day of sampling of the gastric juice (Table I.) It is assumed that at the time the gastric juice is sampled the I^{131} albumin in the circulating blood has reached equilibrium with that of the extravascular tissues, and therefore albumin that exudes from the blood into the gastric lumen thru a mucosal defect should contain the same proportion of free iodine to bound iodine as existing in the blood prior to exudation.

Since the gastric juice samples were not analyzed immediately after collection, there was considerable digestive activity on the albumin I^{131} being quantitated so that the fractionation between supernatant I^{131} activity and washed TCA (tricolor acetic acid) gastric juice precipitate does not reflect the true partition at the time of exudation. Because of this, the value of exuded protein bound I^{131} activity in the gastric juice can be obtained from the total radioactivity in gastric juice by applying a correction factor which may be taken from the partition coefficient of bound iodine in circulating blood (Table I).

Another possibility. is to consider whole gastric juice radioactivity as reflecting the changes in protein bound radioactivity since both fractions run parallel decay curves. The values of I^{131} in gastric juice are expressed in terms of total radioactivity or as corrected radioactivity. The results in the three groups of animals in which 3 types of gastritis were experimentally induced, are given in the following table, in which animals No. 1, 2 and 3 were treated with diol-creosote solution, number 4 and 5 were treated with atophan, and number 6 and 7 received croton oil, alcohol ether mixture:

The amount of gastric juice secreted by the experimental animals before and after gastritis is given in the next tabulation (Table III).

Disappearance half time of albumin I^{131} in control animals was 7.7 days and in control animals was 5.5 days. Average total radioactivity in the gastric juice of control animals was 0.47% per administered dose and in the experimental animals was 1.66%; the average volume of gastric juice secreted in a half hour from the controls was 66 ml and in the experimental group was 114 ml.

Discussion

We have chosen the procedure of assaying directly in the gastric juice the level of I^{131} albumin secreted during a pre-determined period of time because this test is considered to be the best tool currently available for the demonstration of protein exudation thru the gastric mucosa. Gordon (9) in 1959 used labelled polyvinyl pyrrolidone (PVP) with this purpose because this material is not digested nor re-absorbed once exuded into the gastro-intestinal lumen, and thus can be recovered quantitatively in the stools. This method using PVP has been discarded because of serious objections to its use as a reliable indicator among which are that this substance is partly retained by the reticuloendothelial system; unequalities in size of its labelled molecules cause turnover rates of different degrees according to molecule size, and finally, its different molecular structure from that of serum albumin could conceivably induce a different response to the passage thru the gastrointestinal wall.

Paper electrophoresis has been the technique employed by Norpoth (5), Henning (10), Glass (7) and Gulberg (11). This method has been complemented with immunoelectrophoresis by Oystese (12) and Hurliman (13). These authors have provided good evidence on the excretory pathways and on the partition of the different blood protein fractions eliminated. Hurliman has shown that the normal stomach excretes a small amount of serum albumin and globulin. Only in anacid gastritis and in patients with pernicious anemia the presence of these substances may be shown upon direct examination of the gastric secretion. In stomachs with normal secretion of pepsin and hydrochloric acid it is necessary to neutralize the gastric contents with a buffer solution as it is being produced in order to examine protein exuded. In gastric cancer and in various types of gastritis the amount of proteins usually exuded into the gastric lumen is markedly increased. Thus in the clinical picture of "hypercatabolic hypoproteinemia" produced by severe protein loss thru the gastric wall, the electrophoretic pattern shows a characteristic increase in the region of the alpha globulins.

The technique of electrophoresis yields information mainly of a qualitative nature. This was a limiting factor in its application to our investigation. More recently the use of intravenous RISA in combination with the oral administration of the ion exchange resin amberlite Cl (5 grams q.i.d.) has been advocated for the study of protein loss into the gastrointestinal tract. The liberated I^{131} is bound by the resin, which is then assayed in the stools. This method has been described in the works of Seejeekhoy (14), Jone (15), Sum (16), Jiménez Díaz (17), and Lizoro (18). With this method one is able to detect 80% of the excreted I^{131}. However, not all I^{131} gets into the gastrointestinal tract direct from protein loss, for some is excreted by way of saliva and bile. The reason for not using this method is because of its lack of selectivity when one wishes to obtain only the gastric juice I^{131} exudation.

The previous quoted authors (7), (10), (13), (14) have obtained evidence of the effect of protein dissociation of the gastric juice on the freshly secreted (exuded) protein into the gastric lumen. Because of this, we chose not to precipitate the albumin. It has been reported that the I^{131} in the secreted and then subsequently hydrolyzed a albumin was in the form of polypeptides tagged with

TABLE II: I^{131} ACTIVITY IN GASTRIC JUICE AND BLOOD

			I^{131} Per ½ Hr. Gastric Juice % Dose			
	RISA Halftime		Control		Experimental	
Animal	Control	Experimental	Total Act.	Corrected Act.	Total Act.	Corrected Act.
1	9.0	6.2	0.16	0.16	2.41	2.29
2	8.2	5.4	0.69	0.66	1.91	1.76
3	6.0	4.2	0.57	0.53	0.60	0.56
4	—	6.0	—	—	1.03	0.98
5	—	6.2	—	—	3.2	3.04
6	—	6.6	—	—	1.3	1.24
7	—	4.1	—	—	1.2	1.14
Average	7.7	5.5	0.47	0.45	1.66	1.57

I^{131}, tagged thyroxine, and inorganic I^{131} (7, 10, 13, 14). Iodine radioactivity in the gastric juice of the three types of experimentally induced gastritis showed a significant increase as compared with levels obtained in the control animals. The blood disappearance curves of albumin I^{131} demonstrate a persistent parallel between total levels of blood radioactivity versus protein bound activity. Based on this evidence, it may be assumed that the increment of total activity of I^{131} in the gastric juice reflects the excretion of albumin thru the gastric mucosa. It was also observed that the increase in gastric juice activity occurred in association with a shortened turnover time of labelled albumin in the serum of experimental animals.

The correlation of these two facts (gastric juice level, and blood disappearance time) is indicative of the augmented loss of albumin thru the stomach in the above described types of experimental gastritis.

In line with the reports of authors already quoted the loss of albumin thru the gastric wall is an established fact in various types of human gastritis such as: hyperplastic, giant, atrophic and also in the acute exacerbations of superficial gastritis the demonstration by us of abnormal losses of albumin in certain types of experimental gastritis in

TABLE III: VOLUMES GASTRIC JUICE SECRETED

Type of Gastritis	Animal	Volume Gastric Juice	
		Before	1/2 Hour After
Diol-Creosote	1	25 ml	72 ml
	2	50 ml	218 ml
	3	123 ml	160 ml
Atophan	4	—	60 ml
	5	—	144 ml
	6	—	34 ml
Croton	7	—	111 ml
Average		66 ml	114 ml

dogs, is a relevant finding for extrapolation to clinical experience. Dogs are probably the experimental animals that possess stomachs with the greatest resistance to injury.

It may be very likely that patients with chronic gastritis living in this medically conscious world ingest by prescription or self medication with relative frequency medications containing gastric irritants such as aspirin or antirheumatics in general, expectorants, vitamin-mineral combinations (Iron, Copper), may suffer exacerbations of their gastritis with the occurrence of greater protein losses in the gastric secretions. This hypercatabolic loss taken in association with the incomplete protein deficient diets taken by these patients for self relief of their digestive distress, are the main factors underlying the malnutrition often seen in the patients suffering from chronic gastritis.

Summary

In three groups of dogs, three types of experimental gastritis have been produced and studied: (1) "Serous" type with Creosote-Diol. (2) "Erosive" with Atophan. (3) "Papillomatous" with Croton Oil.

In all animals investigated with intravenous RISA, the I^{131} albumin blood turnover curve and the I^{131} appearance in the gastric secretions per unit time were obtained. Results have been compared with normal (control) dogs with the demonstration of increased turnover of albumin from the blood in association with significant in-

crease of labelled albumin in the gastric juice collected, much greater and above that augmentation of protein bound activity that could be explained merely on the basis of an increased volume of secreted gastric juice

Resumen

Se han producido en 3 grupos de perros tres grupos de gastritis: 1) "Serosa" con creosota. 2) "Erosiva" con atofan. 3) "Papilomatosa" con aceite de croton.

En todos ellos se ha realizado a la prueba de inyección intravenosa con albúmina I^{131} (RISA) midiendo el "turnover" en suero y la eliminación por la mucosa gástrica.

Los resultados se han comparado con perros normales resultando que los perros gastríticos tienen un "turnover" más rápido y aumenta la excreción de albúmina I^{131} por la mucosa gástrica.

Es muy probable que en los humanos gastríticos crónicos, que como cualquier humano que vive la medicina presente ingiere con relativa frecuencia medicamentos que contienen aspirina y antirreumáticos en general, balsámicos expectorantes y minerales de Fe y Cu sufran agudizaciones de su gastritis con mayores pérdidas de albúmina a través de su mucosa gástrica. Este hipercatabolismo, unido a las inadecuadas dietas en que se refugian estos pacientes para disminuir las molestias digestivas, son factores principales de la mala nutrición de gran parte de los gástricos crónicos.

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SECONDARY MALABSORPTION SYNDROMES

Nosologic and Diagnostic Aspects

Henry L. Bockus, M.D.

I should like to express my deep sense of appreciation for being permitted to have my name associated with that of Dr. Bailey K. Ashford by being selected as the seventh Ashford lecturer. My decision to discuss malabsorption was dictated primarily by the basic interest in and pioneer contributions to this facet of medicine by the man we are honoring here tonight. Actually tropical sprue, one of Dr. Ashford's primary interests, was that type of malabsorption first described in medical literature. Aretaeus the Cappaducian (2nd century A.D.) (4) has been credited with an early description of something simulating tropical sprue. In 1669, the Dutchman, Vincent Ketelaer (79) described a sprue-like syndrome evidently associated with steatorrhea. However the first clear account of the tropical sprue syndrome was that of William Hillary (1799) in his "Observations on the Changes in the Air and the Concomitant Epidemical Diseases in the Island of Barbados"(68). In 1880, both van der Burg (Java) (125) and Manson (China) (87) independently described the disease that Hillary had reported one century earlier.

From the Graduate School of Medicine, University of Pennsylvania.

Seventh Bailey K. Ashford Memorial Lecture delivered at the University of Puerto Rico School of Medicine, San Juan, Puerto Rico, December 8, 1965.

The name Ashford has been associated with sprue as it occurs in Puerto Rico by all interested persons. The reasons for this are well known to this audience; they have been reviewed by previous Ashford lecturers, some of whom were privileged to have known Dr. Ashford intimately and to have worked with him. His discovery of *Ancylostonum duodenale* as the cause of severe anemia prevalent among the rural population of this island in 1899 and the founding of the Puerto Rican Anemia Commission to combat that disease constitute his earliest major achievements. His role in the founding of the famous Escuela de Medicina Tropical was of equal importance and his unselfish devotion to this school to the time of his death mark a career of service not excelled by any physician of his era. He represents the pinnacle of humanitarian service in this beautiful island—a figure that all devoted Puerto Rican physicians may well try to emulate.

Perhaps the first clear distinction between sprue, as it occurs in the tropics and steatorrhea of nontropical origin was that of Samuel Gee. In 1888 he published a classic description of the coeliac affection occuring both in children and adults. There followed many articles dealing with nontropical sprue or the adult coeliac affection. Those of Holmes and Starr(69) and Thaysen(121) are frequently quoted. In 1932 Bennet, Hunter and Vaughn(16) introduced

the term idiopathic steatorrhea to distinguish the adult celiac affection from pancreatogenous steatorrhea. The major break-through in the pathogenesis of the celiac affections occurred in 1954, when Dicke, Weijers and van de Kamer (39) showed that the noxious agent was in the protein or gluten fraction of wheat, hence the term "gluten-induced enteropathy".

Classification

This task of reviewing the nosologic and diagnostic aspects of the secondary malabsorption syndromes is a gigantic one. I can offer only a panorama. We shall first attempt to deal with a classification of malabsorption syndromes The *sine qua non* of malabsorption is steatorrhea. Clinically, steatorrhea marches across the whole field of medicine in much the same way that syphilis did at the turn of the century. It is a convenient and reliable marker of intestinal insufficiency. Always in mind, however, must be that it is a manifestation of *panmalabsorption,* being associated commonly with a number of nutritional deficits and great variety of symptoms and signs (7). This serves to emphasize a need for nosological clarity, as much as that can be achieved in light of our present knowledge. Progress has been made in this respect. Now it seems appropriate to use the designation *malassimilation* syndromes to embrace all of those conditions characterized by an inability to normally assimilate into the body fluids the ingested nutriment. A broad division may then he made into *malassimilation* due to: 1) digestive defects or impaired hydrolysis (e.g. pancreatogenous steatorrhea); and 2) that the result of defects in absorption or impaired intestinal mucosal transit from gut lumen to body fluids (malabsorption syndromes).

Conditions giving rise to defects in digestion are listed in Table I. With these we are not primarily concerned tonight. In the differentiation of the steatorrheas, by utilization of d-xylose absorption, starch and glucose tolerance tests, fecal analysis, x-ray, jejunal biopsy the secretin test and clinical appraisal, ordinarily it is not difficult to distinguish those due to defects in hydrolysis from the true malabsorption disorders. However, it is not an easy matter to accurately classify the true malabsorption syndromes. A grouping is given in Table II. It has been customary to set aside several of the well known types of

TABLE I:
MALASSILIMATION SYNDROMES
DIGESTIVE DEFECTS —
IMPAIRED HYDROLYSIS

A.	Pancreatic Insufficiency
	Chronic pancreatitis
	Carcinoma of pancreas
	Pancreatic fistula
	Postpancreatectomy
	Cystic fibrosis
	Gastric Secretory — stimulating islet-cell tumor
B.	Hepatobiliary (bile salt deficiency)
	Obstructive jaundice
	Hepatitis
	Cirrhosis
C.	Gastric (impaired hydrolysis)
	Postgastrectomy
	Postgastroenterostomy
	Vagotomy + above operations or pyloroplasty
D.	Prolonged Dietary Protein Deficiency + Pancreatic Acinar and Enzyme Deficiency (Kwashiorkor Syndrome, Marasmus)

TABLE II: MALASSIMILATION SYNDROMES
ABSORPTION DEFECTS — IMPAIRED MUCOSAL TRANSPORT

A. Primary Malabsorption

Celiac affection (Gluten enteropathy — children)

Idiopathic steatorrhea — Nontropical Sprue (Adult gluten enteropathy)

Tropical sprue

B. Secondary Malabsorption

1. Anatomical Decrease in Area of Intestinal Absorption
   - Enteric resections
   - Fistulas (Gastro-jejuno-colic) (Cholecystocolonic)
   - Gastroileal anastomosis
2. Infiltration of Intestinal Mucosa and/or Blockage of Lymphatics
   - Regional enteritis
   - Tuberculosis, (ulcerative, hyperplastic, tabes mesenteric)
   - Intestinal granulomas
   - Lymphomas, lymphosarcoma, Hodgkins disease, etc.
   - Carcinoid tumor with metastasis
   - Carcinoma (Intestinal or mesenteric metastasis)
   - In Systemic Disease
   - Whipple's disease, amyloidosis
   - Collagen disease (systemic sclerosis), sarcoidosis
   - Pneumatosis (cystoides) intestinalis
   - Systemic mast cell disease (urticaria pigmentosa)
   - Acanthocytosis (beta lipoproteinemia)
   - Infectious mononucleosis
   - Schonlein-Henoch purpura, rosacea
3. Mesenteric Vascular Insufficiency — Chronic mid-gut ischemia
   - Vascular occlusions
     - Atherosclerosis
     - Polycythemia Vera
     - Thromboangiitis obliterans
4. Endocrinopathies
   - Diabetes mellitus (diabetic steatorrhea)
   - Hypoparathyroidism
   - Addison's disease (adrenal cortical hypofunction)
   - Pituitary insufficiency
5. Steatorrhea of Bacterial Origin (Competition for Vitamins or Lack of Their Synthesis)
   - Blind loops, jejunal diverticulosis
   - Strictures; partial intestinal obstruction
   - After recovery from acute intestinal infection
6. Parasitic Infestations and Intestinal Infections
   - Giardiasis
   - Uncinariasis
   - Strongyloides
   - Candida (?), Coccidiodes (?), Proteus (?)
7. Protein Abnormalities
   - Hypercatabolic protein-loosing enteropathy-intestinal lymphangiectasia
   - Menetrier's disease with steatorrhea
   - Hypogammaglobulinemia
8. Avitaminosis and Primary Malnutrition
   - Pellagra
   - Brown bowel syndrome
   - Kwashiorkor
   - Marasmus
9. Iatrogenic Causes
   - Radiation injury
   - Antibiotics: chlortetracycline, chloramphenicol, penicillin, neomycin
   - Steroids
   - Cholestyramine
   - Mer 29
   - Phenindione ("dindevan")
10. Miscellaneous
    - Congestive heart failure, constrictive pericarditis
    - Defective lactose absorption
    - Disaccharidase deficiency
    - Gastric secretory-stimulating islet-cell tumor.
    - Sjogren's syndrome

malabsorption under the designation of "Primary," those not due to an underlying disease. These comprise celiac disease (children), adult celiac disease (nontropical sprue; idiopathic sprue) and tropical sprue. The first two are now thought to be the result of a so-called gluten-induced enteropathy attributed an hereditary absence of a specific peptidase essential either: 1) to the digestion of gliadin (toxic fraction of gluten) or 2) to merely an unusual inherent mucosal sensitivity to the polypeptides of gluten. Even now, the true cause of tropical sprue, if indeed there is one pathogenetic mechanism, remains unknown. The various mechanisms that have been considered to be causative have been ably studied by a number of eminent Puerto Rican physicians in this audience (5, 15, 25, 27, 54, 60, 98).

All of the remaining conditions associated with steatorrhea or panmalabsorption are usually termed "secondary malabsorption syndromes." It is with these that we shall concern ourselves. Because of constantly increasing interest in and awareness of steatorrhea, and as a result of more precise technical methods of investigation the list is indeed a long one. It surely see many new additions in the coming decade, for there remains a number of instances of steatorrhea that defy classification at present, *e.g.,* the case recently reported by Naish (95) of intestinal pseudoobstruction with steatorrhea.

Difficulties in classification are due in part to a lack of knowledge of the precise mechanism responsible for many of the secondary types of steatorrhea, even though the morphological or disease status is known. This is certainly true of congestive heart failure (78,102) and hypogammaglobulinemia (30,75). Turner and Williams (124) recently commented on the unexplained steatorrhea in the syndrome of hyponatremia and carcinoma of the bronchus. Indeed the mechanism actually causing the steatorrhea in many of the secondary malabsorption syndromes remains an enigma.

In Table II, Part B, I have listed in 10 categories the reported instances of so-called secondary malabsorption on the basis of supposed mechanisms and/or morphological or disease state. Fifty-three different disorders associated with steatorrhea are included. It may be seen that this is far from a satisfactory classification. In many disorders one may well ask: Does the cause lie in the mucosal cells (enzymatic)? Is it submucosal? Is it due to obstruction of lymphatic channels? How frequently is the blood supply at fault? Or is the trouble intraluminal, (bacterial, toxic, viral, parasitic)? Of interest are the the recent reports (72a, 130) of a protein-losing enteropathy and steatorrhea in association with constrictive pericarditis attributed to lymphatic obstruction and dilatation and changes in lymph flow. Time will not permit a discussion of the various mechanisms thought to be causative in the different secondary steatorrheas. Evidently more than one causative mechanism is active in many of the secondary steatorrheas and frequently it is impossible to determine which one has been primary, *e.g.,* the mechanism of steatorrhea in Whipple's disease may be basically submucosal, an obstruction of lymphatics, yet recently rod-shaped structures in electron micrographs of the lamina propria of the small intestine suggest a viral or bacterial cause (30). In some instances the condition listed may be secondary to the steatorrhea and not actually causative, *e.g.* some of the endocrinopathies and avitaminoses. Many of the disorders responsible for the steatorrhea are exceedingly rare, such as acanthocytosis

(65), pneumatosis intestinalis (36), and systemic mast cell disease (11). Others, not so rare, are infrequently associated with steatorrhea, *e.g.*, diabetes mellitus (18), congestive heart failure (73), giardiasis (26, 96, 120), radiation injury (43, 58, 111) and mesenteric insufficiency (74). Steatorrhea was associated with only 8.5 and 2.3 percent respectively of primary and secondary amyloid (67). Up to 1953 there were only 16 cases of steatorrhea secondary to lymphoblastoma in the literature (117).

On the basis of frequency or unusual interest or both perhaps the following should be mentioned particularly: regional enteritis, tuberculosis, Whipple's disease, collagen disease, lymphomas and other neoplasms, reduced absorptive surface, mesenteric vascular insufficiency, steatorrheas of bacterial origin (blind loops, jejunal diverticulosis, intestinal strictures) and some of the iatrogenic causes.

Diagnosis in Malabsorption Syndromes

Although steatorrhea almost never occurs as a single manifestation of malabsorption, it is the key factor from the standpoint of diagnosis. However, there have been ample reports of the accidentaly or unsuspected discovery of steatorrhea as a result of objective studies. Parker and Ross surveyed 230 asymptomatic adults in order to determine the frequency of unsuspected steatorrhea, and found it to occur in 2.3 percent of persons. Serum carotene determinations were utilized for preliminary screening and this was followed by fecal fat studies in positive cases. Ordinarily steatorrhea is suspected from the history and description of the stools. The easiest method of detecting steatorrhea, and as reliable as any, is that of the gross and microscopic examination of the feces by an experienced person. Rather recently Drummey, et al (Boston) (42) have added further confirmation to the efficacy of this method by its comparison with chemical fecal fat studies. They reported an accuracy of fecal microscopy of 94 and 100 percent in moderate and severe steatorrhea respectively. For confirmation and more accurate measurement of malassimilation of both fat and protein, the fat and nitrogen chemical balance study remains the most precise technique (101). The more recently introduced I^{131} fat studies (using both fecal and blood peak radioactivity) does not afford as adequate a quantitative measurement of steatorrhea as the fecal chemical balance study (100). It is being used as an initial screening method in many clinics. I believe its accuracy is no greater than that of the fecal microscopic study.

Steatorrhea often poses a fascinating and puzzling problem in differential diagnosis Maldigestion or impaired hydrolysis, as a cause of malassmilation and steatorrhea ordinarily presents no great difficulty. Furthermore with the utilization of recent techniques one can usually decide whether the steatorrhea of malabsorption is of the primary or secondary type. However many pitfalls do exist, e.g. amyloidosis may occur as a complication of nontropical sprue (12). The basic cause nevertheless can most often be determined. Badenoch (Oxford Series) (9) was able to classify all but 3 of 163 cases of steatorrhea (Table III). It is unlikely that this diagnostic accuracy has been bettered in the study of any other large group of patients. Of interest is the much greater frequency of the primary malabsorptions in his cases. Idiopathic steatorrhea (including celiac affection) and tropical sprue comprised approximately 70 percent of the cases of steator-

TABLE III: DIAGNOSIS IN 163 CASES OF STEATORRHEA (Badenoch - Oxford Series)

Disease	Number
Idiopathic steatorrhea (onset in childhood 32)	106
Regional ileitis	11
Pancreatic disease	8
Gastric operations	8
Diverticulosis of the jejunum	8
Tropical sprue	7
Tabes mesenterica	4
Blind loops of intestine	3
Gastro-colic + ileo-colic fistulae	2
Mesenteric thrombosis	2
Whipple's disease	1
Unclassified	3
Total	163

rhea. If the 16 cases, the result of defects in digestion (impaired hydrolysis) are excluded, primary malabsorption comprised 80 percent of the malabsorption syndromes.

It is doubtful if this high ratio of primary to secondary malabsorptions will be maintained in future reports because of: 1) frequent cures of the primary types with gluten-free diet, folic acid, etc.; and 2) recognition of many of the secondary types due to increased awareness and improved diagnostic techniques.

The frequency of the primary types of malabsorption in the series of Badenoch greatly exceeds that at the Graduate Hospital because of our greater number of admissions for regional enteritis, enteric resections, lymphomas and fistulas, etc.

Exclusion of Primary Malabsorption

Actually, after ruling out maldigestion (hydrolysis), the exclusion of the primary types can usually be accomplished. The celiac affection (nontropical sprue) is suspected in children and young adults who lack findings to suggest systemic disease or infection. The history of diarrhea is often a long one. In 30 percent of Badenoch's cases the history dated from childhood. However, diarrhea may occasionally be absent (31). Physical findings are often negative except for abdominal distension and findings the result of mal- or subnutrition (wasting, anemia, edema, evidences of avitaminosis, occasionally tetany, etc.). Confirmation is afforded by the presence of the so-called *nutritional deficiency pattern*. Perhaps its most characteristic feature is that of jejunal dilatation simulating the configuration of paralytic ileus, (84, 88). The greater the steatorrhea, and the more severe the symptom configuration, the greater the degree of subtotal atrophy, and of jejunal dilatation (84). Depressed serum potassium and serum magnesium levels were always associated with jejunal dilatation. Other features of the "nutritional pattern" comprise coarsening and irregularity of the Kirkring folds, evidences of excessive mucus secretion, segmentation and flocculation of barium, and at times the moulage configuration. The roentgen deficiency pattern is usually present in nontropical sprue but may occasionally be absent (84). Unfortunately a simulation of this pattern, actually either not close or frequent, has been reported in some secondary malabsorptions (Table VII) (119, 126) including the lymphoma-Hodgkins family (Fig. 1), intestinal lymphangiectasia, Whipple's disease (29, 40, 63,) systemic sclerosis

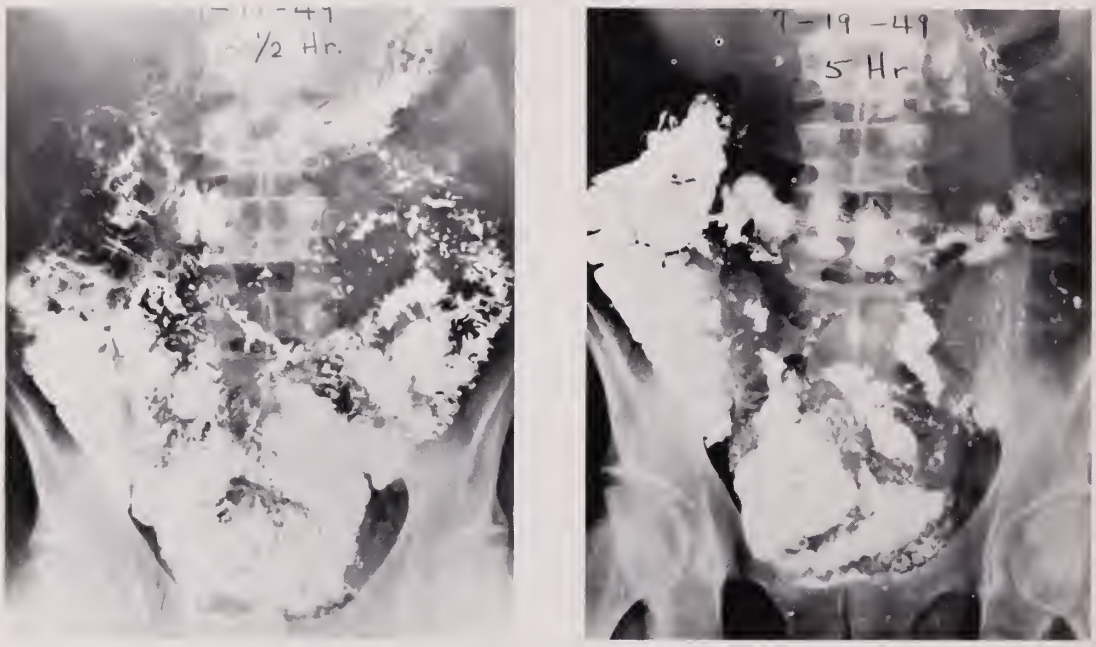


Fig. 1: Nutritional deficiency pattern in 49 year old male with Hodgkin's disease.

A. 2-1/2hours after ingestion of barium showing flocculation, coarsening of Kerckring's folds and ileal dilatation.

B. At 5 hours, showing flocculation, segmentation in jejunum and dilatation and stasis in ileum.

(113), amyloidosis (12, 67) and regional enteritis. However, these secondary malabsorption syndromes that may exhibit a roentgen "deficiency pattern" should present little diagnostic difficulty as biopsy and other specific tests and concomitant roentgen patterns will usually make the diagnosis.

Per oral jejunal biopsy (Table VI) affords confirmation for the diagnosis of nontropical sprue in most instances. Although we cannot concern ourselves with jejunal biopsy techniques or even the minutae of histologic configurations, the characteristics of the biopsy histology in the celiac-sprue syndrome will be briefly mentioned. They include a barren knobby mucosal surface devoid of normal villi, and a widely spaced and irregular vascular pattern. Varying degrees of villous atrophy, subtotal and partial, is a characteristic feature (115). Greatly increased mucosal thickness is noted due to a striking increase in glands. Gland acini seem to be doubled in number. The mitotic rate per 1000 glands is significantly increased. For identical squares of bowel (measured at the muscularis mucosae), the surface area in celiac-sprue subjects is only one-fourth that of normals (25). An increased lymphatic infiltration of the villous surface epithelium is present in most cases. There is a marked reduction in the height of villous epithelial cells with irregularity in shape and arrangement of their

TABLE VI: JEJUNAL BIOPSY

1. Celiac-sprue Pattern → Primary Malabsorption
   Simulation in Secondary Malabsorption (?)
   - Amyloidosis
   - Lymphoma
   - Whipple's disease
   - Lymphangiectasia
   - Acanthocytosis
   - Regional Enteritis

2. Pattern Characteristic of Specific Disease (Secondary Malabsorption)

Lymphoma	Amyloid
Whipple's disease	Sarcoid
Acanthocytosis (?)	Collagen disease
Lymphangiectasia	Regional enteritis

nucleii. Perhaps some of you may not agree with Schenk et al that it is possible actually to distinguish tropical from non-tropical sprue by differences in mucosal height, the pattern of lipid distribution, and the activity of certain epithelial enzymes.

Simulation of the histologic configuration of the celiac-sprue syndrome has been recorded in several of the secondary types of malabsorption. Amyloidosis has actually been reported as a complication of nontropical sprue. (12) It should be suspected with evidence of peripheral or other neuropathy and rectal biopsy is recommended for confirmation (67). The lymphomas may simulate the histologic configuration of the celiac affections occasionally (117) and present real difficulty in differential diagnosis as the roentgen pattern may likewise suggest a sprue-like state. Peripheral lymph node biopsy, failure to respond to a gluten-free diet and exploration may be the order of procedure in these cases. The jejunal biopsy specimen and the roentgen pattern (40) in Whipple's disease may be highly suggestive of a primary malabsorption. The diagnosis of Whipple's disease is now relatively easy with the PAS staining and the imprint techniques (64) and peripheral lymph node biopsy. The simulation of the sprue-type jejunal biopsy by hypercatabolic protein loosing enteropathy (intestinal lymphangiectasia) is close (126).

Here the diagnosis is made by demonstration of increased albumin loss through a rapid degradation of intravenously administered radioactive iodine-labeled human serum albumin (RISA), with a significant decrease of the normal half-life and b) increased fecal excretion of I^{131} labeled polyvinylpyrrolidone (PVP) (126). Occasionally regional enteritis may account for a duodenal or jejunal biopsy resembling that of a primary malabsorption. Ordinarily the simulation is not close. In regional enteritis the mucosal abnormality is usually patchy and disease of the duodenum and upper jejunum is relatively rare. However a superficial resemblance to the celiac-sprue biopsy may occur (33). Rubin et al describe ileal biopsies, via ileostomy, in regional enteritis, showing a marked resemblance to the celiac-sprue pattern. The roentgen pattern in regional enteritis usually is diagnostic. Thus it may be said that the histologic abnormality of the intestinal mucosa is highly characteristic of, but not absolutely specific for, primary malabsorption (83).

The final diagnostic maneuver in suspected non-tropical sprue is improvement on a gluten-free diet which ordinarily clinches the diagnosis. Reactivation of the disease with the administration of gluten adds further confirmation.

The features of tropical sprue are better known by all of you here in Puerto Rico. I

have no desire to bring coals to Newcastle. It is my impression that the roentgen nutritional deficiency pattern and jejunal biopsy findings closely simulate, but being perhaps less striking, than those of nontropical sprue. History of residence in the tropics, glossitis, macrocytic anemia, and defective absorption of folic acid are, I believe, almost universally present. Failure of response to gluten-free diet has commonly been noted, although Bayless reported clinical improvement in 8, decreased malabsorption in 7, histologic improvement in 5 and clinical remission in 4 of 10 Puerto Rican patients with moderate to severe tropical sprue. This evidently had not been the experience of most observers. (53, 54). Rapid response to folic acid or B12 completes the differentiation of tropical and nontropical sprue.

Enough has been said I think to indicate the relative ease with which the primary malabsorption states can be excluded in the diagnosis of the steatorrheas due to malabsorption. When this is satisfactorily accomplished there remains only the steatorrheas of the secondary type since maldigestion (faulty hydrolysis) presumably has been excluded.

Malabsorption in Regional Enteritis

Obviously time will not permit of a detailed account of all of the varieties of secondary malabsorption. Before proceeding with the differential diagnosis, I should like to review in some detail the malabsorption commonly associted with regional enteritis. It is the type with which I have had the greatest experience and the one in which the steatorrhea and evidences of the panmalabsorption have been analysed in the Graduate Hospital clinic. The diagnosis of regional enteritis ordinarily can be made by roentgen study. Negative x-ray by barium enema (with ileal reflux) and progress meal study in patients with steatorrhea may be said to exclude a diagnosis of regional enteritis. The study of malabsorption in regional enteritis permits of a discussion of many aspects of the steatorrhea syndromes common to many of the other secondary types of malabsorption.

For example, it will be seen that almost all of the known mechanisms commonly held responsible for a secondary type of steatorrhea may be encountered in patients with regional enteritis. These include:

1) Obstruction of lymphatic channels. Lymphatic hyperplasia and obstruction to lymph flow is thought to be an early manifestation, if not an important pathogenetic factor in this disease. (3)

2) Reduced mucosal absorptive surface. This is due to:

a) long lengths of diseased bowel and/or
b) surgical resections of varying lengths of small intestine or
c) rarely, the occurrence of internal fistulas.

3) Secondary mucosal disease. This has been suggested by peroral biopsy in some cases (108), perhaps interfering with mucosal transit. Certainly changes in intraluminal environment, of which there is ample proof in many cases of regional enteritis, can alter the pattern of cell turnover and the structure of villi (35). Slight improvement in steatorrhea on a gluten-free diet has been reported in a few cases suggesting the presence of an absorptive defect similar to that of so-called nontropical sprue. It should be mentioned that this is a rare happenstance and may indicate merely the concomitance of an inherent mucosal defect unrelated to

regional enteritis.

4) Stenotic areas of partial obstruction. Here we have a mechanism permitting of bacterial proliferation and bacterial floral changes similar to those occurring in blind loops and jejunal diverticulosis (104).

5) Surgically created blind loops. Side-to-side and end-to-side anastamoses with or without resection create bacteriological situations similar to that created by stenotic areas (as in 4).

6) Chronic diarrhea. Hypermotility per se may not interfere with mucosal transport (101) but when occurring in association with long lengths of diseased bowel or shortened intestine and absence of the ileocecal valve as a result of operation, diarrhea may certainly worsen the nutritional deficiency.

7) Hypermetabolism. Cellular nutrition may be depleted as a result of prolonged fever in some cases perhaps interfering with normal mucosal transport.

8) Endocrinal abnormalities. Nutritional deficiency, particularly in childhood entails in some instances secondary pituitary-adrenal-gonadal insufficiency (intestinal infantilism) that may well further interfere with intestinal function. The stress of pregnancy may induce hypopituitarism (82).

9) Liver and pancreatic insuffiency. Chronic hepatitis and chronic pancreatitis occasionally occur in regional enteritis. A deficiency in bile salts or pancreatic enzymes may aggravate an already existing steatorrhea.

Surely it may be said that in regional enteritis more that in any other secondary malabsorption there exists the possibility of encountering most of the known mechanisms for malabsorption. Furthermore steatorrhea is a frequent concomitant of extensive regional enteritis. It almost never occurs as a single manifestation of malabsorption, being accompanied in many instances with several of the following deficiencies: anemia (usually iron deficiency, occasionally macrocytic in type), hypoproteinemia (particularly hypoalbuminemia), hypoprothrombinemia, hypocalcemia, hypomagnesemia, electrolyte deficits, avitaminoses, and intestinal infantilism (hypogonadism, hypopituitarism, hypoadrenalism). The nutritional status of advanced regional enteritis may indeed be labeled an example of *panmalabsorption*. The nutritional deficits are quite similar to those of the celiac-sprue syndrome.

In the 37 patients reported by Pimparker et al (99) (Graduate Hospital) the diagnosis of all but one was proved at operation (The roentgen configuration was unmistakable in the remaining case). The studies comprised fecal fat and nitrogen chemical balance studies (all patients)* I^{131} triolein absorption tests (18 cases), oleic acid I^{131} absorption tests (7 cases), Shilling-test (17 cases), bone marrow examination (11 cases), glucose tolerance test (8 cases). Hemograms, serum proteins and, prothrombin determinations serum cholesterol, calcium and electrolyte values were performed routinely. Table IV denotes the original anatomic sites of involvement in these 37 cases. Actually the cases were analyzed on the basis of the grouping given in Table V since many patients had had operative procedures prior to their nutritional studies.

Jejunoileitis — Patients with jejunoileitis

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* *These patients were on a Schmidt type diet. Between 50 and 100 Gm. of fat were actually ingested. The partitioning of fat in the diet was roughly 50% butter fat, 30% animal fat and 20% vegetable fat (corn, cotton seed, olive).*

studied preoperatively (5 cases) had extensive disease averaging one-third of jejunum and the proximal one-half to two-thirds of the ileum. In addition to marked universal steatorrhea (mean of 23.2 Gm. daily) and slight azotorrhea (mean of 4.6 GmN. daily) on the basis of balance studies, deficits were encountered in hemoglobin. (10.2 Gm.), total proteins (4.7 Gm), albumin (2.3 Gm), cholesterol (106 mg.) and calcium. B_{12} absorption was normal in one patient whose entire jejunum was extensively diseased.The steatorrhea was marked, but less than that encountered in the blind loop and tthe enterocolitis cases. The severity of the steatorrhea seemed related more to the extent of ileal rather than to jejunal involvement. All of these patients with extensive jejunoileitis had varying degrees of stenosis and required operation eventually because of partial obstruction. Steatorrhea was likewise universally present in Cooke's cases (32) of jejunoileitis. The extent of ileal involvement (not terminal) and stenotic areas of partial obstruction were probably the important factors responsible for the steatorrhea in these cases.

Terminal Ileum — This study of Pimparker's confirms the findings previously reported by Kalser, et al, (77) and Cooke, (32) that involvement of less than 3 feet of the terminal ileum with intact ileocecal valve does not cause steatorrhea. A slight anemia and minimal deficit in prothrombin were the only evidences of malabsorption in the patients with only terminal ileal disease.

Extensive Ileitis — Resection and Ileoascending Colostomy — Patients subjected to resection of from 3 to 7 feet of terminal ileum and *ileoascending colostomy* invariably had steatorrhea (21.2 Gm.) and azotorrhea (N, 4.4 Gm.) with moderate anemia, hypoprothrombinemia, hypoproteinemia. The severity of the steatorrhea seemed to parallel the amount of ileum resected. The increased wet weight of the stool in this group was associated with greater diarrhea as a result of loss of part of the right colon.

TABLE IV: REGIONAL ENTERITIS ANATOMIC LOCATION

Name of group	Number	Percent
Jejunoileitis	7	19
Terminal ileum	15	41
Terminal ileum and skip ileal lesions	5	13
Enterocolitis	10	27
Total	37	100

From Pimparker, et al. Proc. Internat. Congr. Gastroenterol. Leyden, 1960.

Extensive Ileitis — Resection and Ileotransverse Colostomy — Patients with ileotransverse colostomy (10 cases) with resections varying from 3 feet to the entire ileum exhibited a mean daily fat loss of 22.1 Gm and nitrogen loss of 4.7 Gm. and associated deficiencies quite similar to that recorded following ileoascending colostomy. However 2 of the 10 patients had no steatorrhea. Of the 8 patients with steatorrhea, seven had recurrences of the disease at the time of study. The diarrhea and wet weight of the stool was greater than in the ileo-ascending colostomy group, as one might anticipate.

Blind Loop — Eight patients were studied with postoperative blind loops, in the ileum or colon or both. The steatorrhea (mean daily 34.9 Gm.) and azotorrhea (N., 5.5 Gm.) was greater than in any other group

TABLE V: SUMMARY OF FECAL CHEMICAL ANALYSES IN DIFFERENT GROUPS OF PATIENTS

Group Nº	Grouping of cases	Number of Cases	Fecal wet Weight Gm/day	Fecal dry Weight Gm/day	Fecal Chemical		
					Fat percent Dry Weight	Fat Gm/day	Nitrogen Gm/day
	Normal Controls	24	115	34	14	4	2
I	Preoperative jejunoileitis	5	568	85	32	23	4.6
II	Preoperative terminal ileitis	4	177	31	7	2	1.5
III	Postoperative ileoascending colostomy	5	839	91	22	21	4.4
IV	Postoperative ileotransverse colostomy	10	1032	99	29	22	4.6
V	Blind loop	8*	938	108	31	34	5.54
VI	Eneterocolitis	8	2015	199	20	53	10.3

* *Three of these cases were also studied preoperatively under Group I.*

From Pimparker, et al, Proc. Internat. Congr. Gastroenterol., Leyden, 1960.

except for enterocolitis. Anemia, hypoalbuminemia, hypoprothrombinemia and hypocalcemia were noted. Active disease was present in the blind loop in all but one of 8 cases and this one did not have steatorrhea. The longer the blind loop existed, the greater the steatorrhea. One patient, after the exhibition of antibiotics, and 2 patients following resection of the blind loop showed striking improvement in steatorrhea and nutrition.

Enterocolitis — In 8 patients studied with enterocolitis both before and after operation, great variation was noted in the degree of steatorrhea dependent upon extent of disease and amount of resection. If only the terminal ileum and proximal colon was involved (5 cases) the fecal fat ranged from 3 to 20 Gm., with a mean value of 9.7 Gm. Those with extensive involvement of the ileum and colon had a mean value for chemical fecal fat of 62 Gm. with a range between 20 and 166 Gm. The greater the involvement of the small intestine the more severe the steatorrhea. Obviously diarrhea was intense and wet weight of feces quite high (2015 Gm.) in patients with extensive colonic disease or colonic resection. Electrolyte disturbances were more common in this group.

This review of findings in regional enteritis both pre- and post-operative study affords a good panorama of malabsorption in the secondary steatorrheas. It is well known that absorption occurs primarily in the jejunum. Certainly this is true of sugars, amino acids, and water soluble vitamins. Hydrolysis of carbohydrates and proteins also occurs in the proximal small bowel. Fats are also assimilated in the jejunum. On the basis of analysis of degree of steatorrhea in relation to site and extent of involvement in regional enteritis further data concerning the site of greatest importance in fat absorption becomes available. This study suggests that the ileum is more concerned than the jejunum confirming the observation of Kalser et al (77) and others. Furthermore it was found if the ileum was crudely divided into 4 parts (estimated by x-ray and operative findings) that the third quarter was probably more active in fat absorption than any similar length of the small intestine. In 21 patients in this study the third quarter or more of the ileum was diseased, resected, or by-passed. The mean daily fecal fat excretion in this group was 35 Gm. daily. In the preoperative patient the degree of steatorrhea is dependent not only upon the length of intestinal involvement but the activity of the disease. In the postoperative patient the additional factors of amount of intestine lost by resection and the presence or absence of blind loop are significant. Vitamin B_{12} absorption is frequently abnormal in ileal disease (17 tests on 12 patients) and rarely disturbed in contradistinction to that of folic acid, in jejunal disease. Normal B_{12} absorption in the steatorrhea of regional enteritis should suggest either disease confined to the jejunum or only minimal involvement of the most terminal ileum, rather than extensive ileal disease. Folic acid absorption was not studied. Chanarin and Bennet(28) reported abnormal absorption of folic acid in 19 of 22 cases of regional enteritis. Nineteen patients had undergone resection of part of the ileum—16 patients had resections more extensive than 2 feet. No mention was made of presence or absence of jejunal disease.

The more severe steatorrhea in regional enteritis the greater the liklihood of panmalabsorption with multiple nutritional deficits. Anemia, hypoalbuminemia, hypoprothrombinemia, hypocalcemia and electrolyte deficits

are common accompaniments.

Preoperative fecal balance studies have great prognostic value. Significant preoperative steatorrhea indicates extensive disease. Such patients did poorly postoperatively, both from the standpoint of nutrition and recurrences. However even with very extensive involvement, after resection of long lengths of intestine, which certainly did not increase the total absorptive surface, the nutritional status of some patients showed striking improvement. This suggests that active disease per se in the bowel segment plays an important role in malabsorption as well as the actual reduction in absorptive surface area.

Blind loops. In experimentally-created blind-loops the mechanism of steatorrhea was not clearly established (41a). It could not be attributed to destruction of intestinal mucosa, to impaired lipolysis of triglyceride, or to bacterial uptake of lipid. In our studies in regional enteritis, the blind-loops were diseased and their presence definitely worsened the steatorrhea. Certainly end-to-end anastamosis with resection is the operation of choice. Because of the importance of the right colon in absorption of water, electrolytes, glucose and perhaps vitamins, it is advisable to preserve as much of the right colon as possible in operations for regional enteritis and enterocolitis.

Differential Diagnosis of the Secondary Malabsorption Syndromes

Clinical Data — The hydrolytic defects (maldigestion) and the primary malabsorption syndromes having been excluded, this large group of diseases capable of causing or at any rate of being associated with steatorrhea (the secondary malabsorption) must be in mind. The nutritional aspects of patients with secondary steatorrhea do not differ from those associated with the steatorrhea of the celiac-sprue syndrome or of those just described in severe regional enteritis. In somewhat the order of frequency and importance, modified of course by the responsible disease, they include weight loss, asthenia, diarrhea, abdominal distension and gaseousness, anemia, edema, hypoproteinemia, hypolipemia, hypoprothrombinemia, hypocalcemia, hypomagnesemia, hypokalemia, osteomalacia, and infantilism. As always, a careful clinical appraisal will determine the specific diagnostic studies to be selected. On the basis of a good history and physical examination it is possible to give consideration to a great many of the disorders responsible for the secondary steatorrhea. I shall epitomize a few of these clues to diagnosis in the steatorrheaic patient which should determine the need for specific studies:

1. History of radiation for carcinoma of cervix → *radiation enteritis?* (43, 58, 106, 111)
2. History of chronic lung disease, particularly asthma → *pneumatosis intestinalis?* (36)
3. Elderly patient with cardiovascular disease and suggestion of abdominal angina → *mid-gut ischemia?* (74)
4. Male with initial arthritis, then diarrhea and fever and possibly pigmentation → *Whipple's disease?* (29, 40, 63)
5. Male, short history, weight loss, nontender abdominal mass → *lymphoma?*
6. Non-operated elderly person with intestinal symptoms and unexplained macrocytic anemia → *jejunal diverticulosis?* (34, 104, 127, 133)
7. Diarrhea in brittle diabetic with neuro-

pathy → *diabetic steatorrhea?*(18)

8. History of administration of antibiotics → *altered bacterial flora?*(49, 72, 93)

9. Youth with history of repeated infections → *hypogamma-globulinemia?* (2, 24, 30, 70)

10. Milk intolerance in adult perhaps dating from childhood → *lactose intolerance?*(37, 78, 91, 129)

11. Symptoms of postprandial palpitation, flushing and diarrhea associated with pulmonary heart murmurs → functioning *metastatic carcinoid?*(81)

12. Ulcer-like symptoms with diarrhea and gastric hypersecretion → *islet cell tumor?*(62, 75, 89, 105)

13. Esophageal symptoms, skin changes and abdominal symptoms → *progressive systemic sclerosis?* (90, 107, 113)

14. Youth with peripherial edema, ascites and/or pleural effusion and hypoalbuninemia → *hypercatabolic protein-loosing enteropathy?*(119, 126)

15. Young adult, low cholesterol, spikey red cells → *acanthocytosis?*(65)

16. The association of bleeding with steatorrhea (10 percent of Badenoch's patients) — either hematochezia, epistaxis, menorrhagia, hematuria or purpura, usually related to lack of vitamin K → more common in *celiac-sprue syndrome.*

17. Skin lessions for years, progressive development of bone changes, hepatosplenomegaly and diarrhea → *systemic mast-cell disease?*(11)

18. History of ulcer surgery → *gastrocolic fistula? gastro-ileal anastamosis?*(59) *gastroenterostomy and vagotomy?*(57) *gastrectomy?*

19. History of small bowel surgery → *reduced absorptive surface-resections?*(77, 80)

20. Palpation of abdominal mass → *neoplasm* (lymphoma), *regional enteritis, granuloma?*

21. *Congestive heart failure* with diarrhea.(73)

22. Peripherial lymph nodes enlarged → *lymphoma, Whipple's disease?*

Biopsies:

Jejunal biopsy (Table VI) has achieved an important place in the diagnosis of the malabsorption syndromes. The significance of the celiac-sprue pattern in the primary malabsorption has been discussed and those secondary malabsorption syndromes that occasionally simulate the sprue pattern have been mentioned previously. In some of the secondary malabsorption syndromes the jejunal biopsy may disclose at times the identity of the causative disease. In this category one may include lymphoma, Whipple's disease(40), acanthocytosis, lymphangiectasia, amyloid, sarcoid, collagen disease and rarely regional enteritis. It was hoped that electron microscopy would prove valuable in the study of fine structure of the intestine in diffuse mucosal disease. So far it has contributed significantly to our understanding of only two diseases, Whipple's disease and congenital B-lipoprotein deficiency.(123)

Rectal Biopsy has been recommended as preferable to jejunal biopsy in amyloid disease.(67) *Peripheral lymph node biopsy* may be revealing in lymphoma, Whipple's disease and sarcoid. *Liver biopsy* may be helpful in the diagnosis of sarcoid, metastatic malignancy, lymphoma and amyloid disease.

Routine Fecal Analysis:

Intestinal Bacteria—Aside from studies related to the measurement of malassimilation (fat-nitrogen chemical fecal balance;

fecal microscopy; radioactive fecal fat studies, etc.) routine fecal examination may be of value in the elimination of parasitic diseases, e.g., giardiasis, (7, 26, 96) uncinariasis, (85, 114) and strongyloides(47). Abnormal jejunal mucosal appearances and sometimes malabsorption have been reported to occur as a result of these intestinal infestations. Increased fecal excretion of I^{131}-labeled poly-vinylpyrrolidone (PVP) is diagnostic of hypercatabolic protein-losing enteropathy (intestinal lymphangiectasia). The thesis of autointoxication of Metchnikoff has perhaps recovered something of its status in view of recent studies indicating the importance of intestinal bacteria in vitamin synthesis, and in the malabsorption states the result of blind loops, jejunal diverticulosis, intestinal stenosis, the administration of antibiotics, etc. Steatorrhea has been reported following recovery from acute intestinal infections when antibiotics have not been used.(86) Present concepts exonerate the luxurient pablum of bacteria in the colon. It is the proliferation of organisms in the normally relatively sterile small intestine,(41) that is being given increased importance particularly in relation to the disorders just mentioned. It is well known that the small intestine is rarely sterile in the patient with achlorhydria. Evidenly the feculent flora derives from above the areas of partial obstruction in blind loops, and in jejunal diverticulosis as cultures from below these areas in the intestine yield sterile or scant growth.(20) Unfortunately fecal cultures have no value in these situations and small bowel cultures are not practical as a diagnostic aid.

Roentgenologic Studies:

(Table VII)—Aside from the value of finding roentgen evidences of the so-called nutritional deficiency pattern previously discussed in the diagnosis of primary deficencies, the *barium meal study* remains the most important practical diagnostic aid in the secondary malabsorptions. Significantly diagnostic are the roentgen findings in gastro-jejuno-colic fistula, regional enteritis, jejunal diverticulosis, carcinoma and pneumatosis intestinalis. In the following conditions a roentgen abnormality is commonly detected, but its precise nature may be in doubt: gastro-ileal anastamosis, scleroderma, carcinoid, lymphoma, vascular stenosis (131), radiation enteritis, amyloid, Whipple's disease and sarcoid. The barium meal study may not have the accuracy in diagnosis possessed by jejunal biopsy in a few of the secondary malabsorptions but its overall diagnostic value in this area exceeds that of any single diagnostic technique. *Plain film of the abdomen* may prove helpful initially in providing information concerning bowel obstruction vs. dilatation secondary to malabsorption. Calcifications (pancreatic or bi-

TABLE VII: BARIUM MEAL STUDY

Nutritional Deficiency Pattern → Primary Malabsorption	
Simulated by:	lymphoma, intestinal lymphangiectasia, Whipple's disease, scleroderma, amyloidosis, regional enteritis (?)
Significant Specific Diagnostic Pattern in:	Regional enteritis, gastro-jejuno-colic fistula, jejunal diverticulosis, pneumatosis intestinalis, carcinoma.
Abnormal Pattern But Not Always Specific in:	Gastro-ileal anastomosis, lymphoma, vascular stenosis, Whipple's disease, scleroderma, carcinoid, radiation enteritis, amyloid, sarcoid.

liary), calcified cysts, solid organ enlargement and changes in bone texture (osteomalacia) may be revealed. Retroperitoneal air has been demonstrated in association with pneumatosis intestinalis.(36) The chest film often has value in the patient suspected of having tuberculosis, lymphoma, metastatic malignancy, sarcoid and pneumatosis intestinalis.

Special Procedures:

In certain diseases in the secondary malabsorption family special procedures, other than those already described, are often diagnostic. Some of these are listed in Table VIII.

TABLE VIII: SPECIAL PROCEDURES

Procedure	Disease Suspected
1. Selective mesenteric arteriography	Mid-gut vascular stenosis (13)
2. Shilling test	Blind loop
Bone Marrow Biopsy	Jejunal diverticulosis Intestinal stenosis, etc.
3. Gastric Secretory study	Islet-cell tumor (89,105)
4. Calcium metabolism	Hypoparathyroidism
5. Protein electrophoresis	Hypogammaglobulinemia (2, 56, 70, 75)
6. Biochemical serotonin studies	Metastatic carcinoid (81)
7. RISA intravenously	Protein-losing enteropathy (126)
8. Lactose and glucose-galactose absorption tests	Lactase deficiency (37, 78)
9. Sigmoidoscopy	Concomitant - colonic disease Radiation sigmoiditis

TABLE IX: THERAPEUTIC TESTS

Therapy	Disease
Gluten-free diet	Celiac syndrome
Folic A, B_{12}	Tropical sprue
Antibiotics	Macrocytic anemia Blind loop Jejunal diverticulosis Intestinal stenosis
Steroids	Non-specific

Therapeutic Test:

(Table IX)—In some instances a precise diagnosis in malabsorption will await a trial of therapy. The gluten-free diet in non-tropical and the exhibition of folic acid or B_{12} in tropical sprue are examples. Indeed, failure of response in either case should cause one to look about for other diagnostic possibilities. Response to gluten-free diet should be expected within 4 to 6 weeks and indeed in many patients improvement occurs within a few days. However in some few instances improvement was delayed as long as 6 (55) to 9 months. (32) It should be borne in mind also that occasionally a so-called secondary steatorrhea such as that occuring in regional enteritis, (115) lymphoma, (17) hypogammaglobulinemia, etc. has been reported to have responded to a gluten-free diet. In the secondary malabsorptions broad spectrum antibiotics may have a salutary effect on the macrocytic anemia and steatorrhea in the blind loop syndrome, jejunal diverticulosis and intestinal stenotic lesions.

TABLE X: EXPLORATORY LAPAROTOMY IN STEATORRHEA

Indicated in the presence of:	
Unexplained roentgen abnormality	
Palpable mass	
History commensurate with neoplasm	
Most often required in:	
Lymphoma	Collagen Disease
Carcinoma	Tabes Mesenterica
Carcinoid	Mid-gut vascular stenosis
Islet-cell Tumor	Pneumatosis intestinalis
Partial bowel obstruction	Gastro-ileal anastomosis

Surgical Exploration:

(Table X)—As a last resort, surgical exploration may be required. The presence of a roentgen abnormality in the patient with steatorrhèa of undetermined origin may warrant exploration to exclude lymphoma, carcinoma, carcinoid, islet-cell tumor, stenosis of vascular origin, partial intestinal obtructon, intestinal involvement in collagen disease, gastro-ileal anastamosis, tabes mesenterica, and pneumatosis (cystoides) intestinalis. The ability to palpate an abdominal mass in the steatorrheic patient is a frequent indication for exploration.

Discussion

In the field of gastroenterology, I suspect that greater advances have been made in recent decades in the area of malassimilation than in any other segment of the specialty. From the beginning, steatorrhea has been the key to its recognition, opening the gateway to a better understanding of small intestinal function and disease, which had lagged far behind that of the stomach, liver and biliary tract, and colon. It has been noted that the early studies were carried out on what we now call the primary malabsorption syndromes. A great deal is now known of the mechanism of their production and the various clinical abnormalities for which they are responsible. As a result of increasing awareness of steatorrhea on the part of the clinician and the introduction of more precise techniques for the study of small bowel disorders in recent years a gradually increasing number of patients with intestinal malabsorption not belonging to the celiac-sprue family, have come to light. These have been referred to as secondary types of malabsorption, since the steatorrhea exists as a symptom complex of an underlying disease. It is with these that we have concerned ourselves tonight. It was not possible to classify them accurately on the basis of the causative mechanism for the steatorrhea. We have had to be content with a grouping of cases partially on the basis of the mechanism responsible for the steatorrhea and to some extent on the basis of the underlying disease or disorder. I have stressed the multiple factors that may participate in many instances in the production of these steatorrheas.

Regional enteritis is certainly one of the most frequent causes of secondary steatorrha in some clinics in the United States. It has been found that almost all of the known mechanisms that may be held responsible for the development of malabsorption were present in the various cases of regional enteritis. They were enumerated. This study has indicated that the important items re-

sponsible for the steatorrhea in regional enteritis were length of intestine involved, degree of activity of the disease and stenosis, as well as the presence or absence of blind loops and the amount of resection of the small intestine in the operated patients. This analysis clearly indicated that malabsorption of the secondary type is not manifested by steatorrhea alone. The concomitant nutritional deficits encountered were quite similar to those that have been repeatedly reported in primary malabsorption. So that steatorrhea, regardless of type of mechanism, rarely occurs alone. Perhaps one may be justified in using the term steatorrheic panmalabsorption to emphasize the frequent concomitant nutritional deficits. Anemia, hypoalbuminemia, hypoprothrombinemia, hypocalcemia, hypokalemia are some of the more important accompaniments. Mention has been made of certain nutritional deficiencies specific to some of the rarer forms of secondary malabsorption. Biochemical abberations not commonly measured clinically or understood, *e.g.,* urinay excretion of phosphorylethanol amine (50) and p-hydroxyphenylacetic acid and indole acetic acid(23) as well as mucosal enzyme deficits (mucosal disaccharidases—invertase, maltase, isomaltase, lactase) (14, 103) and sucrase (109) have been reported in the celiac-sprue syndromes and may well exist in the secondary types as well. These enzyme deficiencies have achieved a level of clinical importance. There are probably many other enzyme and biochemical abnormalities associated with the malabsorption states that will subsequently be discovered.

It has been pointed out that the differential diagnosis of primary and secondary malabsorption is ordinarily easy thanks to the highly significant roentgen characteristics, jejunal biopsy findings, and the results of the trial of therapy in primary malabsorption. Nevertheless we have seen that each of these characteristic features of primary malabsorption may be mimicked occasionally by a secondary type. However, a secondary steatorrhea exhibiting all three of these features (commonly found in primary malabsorption) is indeed rarely encountered.

Our concern has been with the precise diagnosis in many of the secondary steatorrheas. I have mentioned the diagnostic features of many of these which often prove helpful, indicating that the clinical configuration and roentgen examination have greatest importance, with biopsy (jejunal, rectal, lymph node and liver) proving diagnostic in some instances. With these measures and the special procedure that were enumerated, usually a definite disease diagnosis can be made. However, there remain some instances where exploratory laparotomy must be undertaken.

We look forward to further exploration by the newer experimental methods for elucidation of steatorrheic mechanisms and for help in therapy. Electron microscopy, biochemical study of biopsy specimens and studies based upon the utilization of isotopically labelled fat have much to offer in this respect. Although Frazer's "partition theory" is no longer accepted, it marked a beginning in the understanding of differences in mechanism of absorption of the various fats. This theory held that the route of fat absorption, via lymph or via blood was determined by whether the fatty acid was pre-

sented to the mucosa in the esterfied or free form, *i.e.,* triglycerides were thought to be absorbed exclusively into the lymph and free fatty acids into the portal blood. Studies with isotopically labeled fats have shown however that the route of assimilation depends largely upon the length of the chain of carbon atoms. Triglycerides containing fatty acids with more than 16 carbon atoms enter the lymph almost exclusively, whereas the short chain fatty acids, 10 carbons or less, entered the portal blood whether they were free of esterified. (19,22,92) More recently hydrolysis of the medium-chain triglycerides has been given increasing attention. (61) These acids are transported via the portal vein as free fatty acids to the liver where they are evidently rapidly metabolized. This knowledge has resulted in the use of medium-chain triglycerides in the treatment of chyluria, chylothorax, pancreatogenous steatorrhea and more recently in tropical sprue (27). Poor absorption of long-chain saturated fatty acids was noted in sprue particularly by Asenjo et al (5). It has been shown recently that in contrast to long-chain triglycerides, medium-chain triglycerides are absorbed efficiently despite diminution in the quantity of available bile acids in the intestinal lumen (brought about by cholestyramine administration). (134)

These brief comments although far from exhaustive on the differential absorption of triglycerides are mentioned to indicate that further exploration of differences in absorption of the various fats may not only add further valuable data in therapy but should supply additional information concerning steatorrhea mechanisms resulting in greater precision in the diagnosis of the various secondary malabsorption syndromes.

Further exploration of microchemical phenomena in the intestinal epithelial cell stimulated by research in malabsorption, may well lead to discoveries that are more basic and far reaching than those concerned only with malassimilation. At any rate, as clinicians, we have become alert to the importance of steatorrhea and its role in the better understanding of intestinal function and disease. We hope to be able to add to our present factual knowledge by careful clinical study of our patients and to be prepared to collaborate with those carrying out basic investigative problems in this broad field. We must have ever in mind in our investigative efforts the need to combine the techniques of Hipborate with those carrying out basic investi- of Galen (basic research).

Finally may I express my sincere appreciation for the privilege of being with you in this capacity tonight. In the name of your distinguished predecessor I charge you with the responsibility of continuing your interest and work in this fascinating area of medicine. I should like to remind you that Puerto Rico is the geographic and ethnic crossroads between the cultures of Latin America and North America. Through your School of Medicine, your School of Tropical of Medicine and I hope in the future, a Graduate arm in Medicine, you have the opportunity of bringing these two cultures with their medical *addenda* closer together. I know you are fully aware of this opportunity for unique service.

Indeed I should like to make a plea for the development of even closer bonds between doctors everywhere. Pasteur has said: "Science has no country." Richard Mead, eminent London physician and possessor of the Gold-headed Cane, adopted as his motto

"non sibi sed toti mundi" — not for himself alone, but for the entire world. (This motto is inscribed over the portals of the home of the Philadelphia College of Physicians.) Albert Schweitzer's dictum beautifully expresses this ideal: "The fellowship of those who bear the mark of pain knows no boundary. They belong together all over the world."

We would like said of us that which was said of Sir William Osler: "that the boundaries of his profession swept the horizons of our globe and he swung along with his brothers everywhere. He saw the *man* under the veneer of traditions and prejudices of boundary lines, and to the *man* he gave his hand

"For there is neither East nor West
Nor Border, nor Breed, nor Birth
When physicians stand face to face
Though they come from the ends of the earth."

May the physicians of Puerto Rico continue to follow in the footsteps of the great Ashford by promoting the philosophy not only to "relieve those who bear the mark of pain" but to support in full measure the preservation of the dignity of man and of the image of God in our world.

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WHAT'S AHEAD UNDER MEDICARE

James Z. Appel, M.D.*

I appreciate this opportunity to discuss with you the new Medicare law which has been described as the biggest social welfare measure in history.

Big it is!

It will touch the lives and paychecks of virtually every American.

It will bring about profound changes in the relationship between millions of older Americans and the sources of health care — their physicians and hospitals.

It will cost 4½ billion dollars a year to start.

It will require the services of from 7,000 to 8,000 new federal employees to administer its provisions.

It will result in steadily rising Social Security taxes between now and at least 1987 to finance its benefits.

It will bring a great new influx of patients into the nation's health facilities, and place increased demands on the time and energies of physicians across the country.

Most significant of all, it will usher in a new era of Federal government participation in a certain aspect of the national life in which it has never been involved before.

In the company of a great many others, the medical profession opposed the principle of Social Security financing of the health care of a large segment of the population without regard to the needs of individuals for financial aid.

We thought it was wrong for a young taxpayer struggling to make a home for a growing family to be required to pay the medical expenses of a retired millionaire. Nor did it seem reasonable for a younger person to pay heavy taxes for 40 or more years without assurance that he would ever realize benefits comparable to the payments made, or even any benefit whatsoever. Unless he lives past age 65 he will receive no benefits for that portion of his Social Security tax that is earmarked for Medicare.

Beyond all this — for we are first and last physicians — our major concern was that the adoption of the program would retard, rather than promote, the science and art of medicine and the betterment of the public health.

However, the long debate is over. Congress has made a fundamental policy decision. It has extended Social Security to cover hospital care for the nation's elderly. At the same time, it has offered to everyone over 65 a government program to help them meet medical expenses, with premiums to be shared by individuals and the Treasury. It has extended the Kerr-Mills Law to cover Hospital and Medical care of the financially needy of all ages.

Delivered before the 63rd Annual Meeting of the Puerto Rico Medical Association, November 9, 1965.

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This action, as it now stands on the statute books, is what occupies us today.

We dare not take it lightly. Medicare is the biggest invasion by the Federal government into health care of all the existing programs, for it affects almost 20 million Americans. Moreover, it also is a program that has the greatest danger of expanding itself to cover the entire population and thus become a national system of health care.

Some may say: "Oh, you're crying 'wolf' again!" Am I?

— On Oct. 20 the ADA (Americans for Democratic Action) indicated that its 1966 legislative program might include a government-supported health insurance plan for anyone who wants it.

— In the Oct. 25 issue of The AMA News a Canadian official was quoted as estimating that within five years 95 per cent of the Canadian population would be covered by medicare, a program which began as a hospitalization program only.

— Recently Sen. Russell Long, the majority whip of the U.S. Senate, said he expects Social Security to be extended to include hospital care for disabled people below age 60 and to widows who cannot find work and who have children to support.

— And we shall not forget Mr. Forand's statement of several years ago: "If we can only get our foot in the door, we can go on from there."

The door is open, but we must see that the chain lock is securely fastened so that the door is not opened wider and wider.

Despite what you may have heard or read, the position of the AMA on medicare is still a firm one. We have not urged our members to give in or surrender to medicare. We believe just as strongly as ever that these medicare proposals, parts A and B, are not in the best interest of the United States.

Under medicare the quality of the care to be provided for those over 65 is in serious danger because of the probable impact of this law on physicians, hospitals, nursing homes and other institutional and individual vendors of health care.

However, your AMA believes that the only statesmanlike and rational behavior is to try — in the most effective way possible — to bring about regulations and other implementations that will mitigate the damaging effects that we know are likely to occur. Your AMA feels that its efforts now must be directed toward preserving and strengthening — to the fullest degree possible — the freedom of physicians, hospitals and other personnel involved in the rendition of the benefits provided.

At the same time we shall exercise our right to criticize the law, any of its sections or regulations, and to urge amendment or repeal when such actions are indicated.

If this is our intent, then indeed we must be responsible, we must be objective, we must be discretionary in all our responses to the development of administrative policies and the actual implementation of the Law. The people of this nation know the law cannot be implemented without the use of the medical profession. Sabotage by non-cooperation will not develop and demonstrate the harmful effects that need correction by amendment or even perhaps repeal. Such non-cooperation will only bring down upon the medical profession the flames of vituperation of the public, fanned by the social planners who promoted this bill in full knowledge of its imperfections and only as a step towards a more radical departure from a free society.

Consequently, an Advisory Committee of

the AMA has been meeting with HEW officials to give advice and guidance in the implementation of medicare regulations. Otherwise, hastily written and unrealistic regulations could aggravate even further the undesirable effect of the law.

While I do not have time to cover all the ways in which Public Law 89-97 will affect you, let's take a brief look at a few of them.

First, of course, is the matter of physician-patient relationship under medicare, or what has come to be known as participation versus non-participation.

Your AMA does not believe that any individual physician should be dictated to regarding his choice of rendering care to patients under the conditions embodied in, or to be written into, Public Law 89-97.

Your AMA House of Delegates said this emphatically when it adopted a resolution which states that the AMA will oppose "any program of dictation, interference, or coercion, whether direct or indirect, affecting the freedom of choice of the physician to determine for himself the extent and manner of participation or financial arrangement under which he shall provide medical care to patients under Public Law 89-97."

On the other hand the medical profession subscribes to a set of principles which point out that under certain circumstances we cannot refuse our services to our patients. In essence, these circumstances occur when our action of refusal would deprive a patient of needed medical care. Medicare is the law. We must obey the law. The law specifically states it is not compulsory that physicians render service under its provisions. But no one should suffer for lack of service.

Each physician must finally decide for himself the course he will pursue — and this the law clearly permits.

So the first effect of the law will depend largely on your decision to participate or not to participate.

Another portion of the law which will affect many physicians is the separation of professional fees and hospital charges, or the sensitive question of the role of pathologists, radiologists, anesthesiologists, and physiatrists in hospital and medical care.

In the law these medical specialists and their services are under Part B, Supplementary Medical Insurance Benefits for the Aged. We hope that they remain there. Only actual Hospital Costs related to these types of services will be billed as Hospital Services under Part A.

However, Sen. Douglas of Illinois has proposed an amendment which would define under Part A the professional services of more than 25,000 practicing radiologists, pathologists, anesthesiologists and physiatrists as "inpatient hospital services." Thus, by federal law hospitals would be authorized to sell the services of these physicians as a hospital service.

A month ago at a special session your House of Delegates made this clear and succinct statement on this issue:

"Hospital-based medical specialists are engaged in the practice of medicine. The fees for the services of such specialists should not be merged with hospital charges. The charges for the service of such specialists should be *established, billed* and *collected by* the medical specialist in the same manner as are the fees of other physicians."

A third area of vital concern is the matter of utilization review committees in hospitals. As you know, there has been a great deal of discussion, with a variety of opinions. as to the purpose of such committees, but there has been general agreement that member-

ship be limited to include physicians only.

Consequently, at its special session your House adopted a statement declaring that "hospital utilization review committees shall be composed of practicing physicians."

To my mind the autonomy of the medical staff of a hospital must be preserved if we wish our patients to receive the kind of care they deserve. The determination of need for, or extent of, health care in a hospital cannot be made by people not knowledgeable in medicine. So the medical staff of the hospital must accept this responsibility. It cannot permit lay people, administrators, social workers, to dictate to the staff on these matters.

I would be remiss if I did not specifically point out the role of the utilization committee in the Medicare Law. This role is not one that would lead to refusal of hospital admission, or decree early discharge of a patient from the hospital. Under medicare the decisions of the utilization committee would merely determine if benefits may be paid and when such payments should terminate.

If the membership of utilization committees indeed are limited to physicians, then a group of second concerns crops up, such as the function of the committees and the cooperation with them by physicians. I personally believe that the utilization committee should be more of an auditing committee than a punitive body. And I believe that we shall need to set up good lines of communication and cooperation with utilization committees. If we do not, I am certain that we could wind up with "outside" appointments to utilization committees — and I definitely mean "non-medical" appointments.

Other areas affected by the medicare law include: compensation for medical services, certification by physicians, and reasonable fees.

On each of these your House of Delegates has taken these positions:

Compensation: The law clearly defines two methods by which the charges for physicians' services shall be reimbursed. One procedure is for the physician to bill his patient whatever charge he considers equitable. The patient pays the bill; the physician gives the patient a receipted bill. The patient then presents the receipted bill to the carrier for reimbursement. Said reimbursement consists of 80% of the benefit provided by the carrier for the type of service rendered after deduction of $50 if such deduction had not already been paid by the patient during that calendar year. You will note that the reimbursement to the patient is determined by the fee schedule of the carrier, regardless of the amount of the physician's bill.

The second method of billing would be that the physician and the patient sign an assignment to the physician. Under this method the same reimbursement, 80% after the deduction of $50, would be paid by the carrier directly to the physician. However, if this method is adopted, the physician's bill must be the same that the carrier lists in its fee schedule. If the patient had not already paid the annual $50 deductible, the physician would have to include with his claim to the carrier, not only the assignment just described, but also a receipt proving the patient actually paid the $50.

In either case the patient would have to pay the 20% co-insurance directly to the physician, based on the total bill less $50 if the deductible provision is applicable.

Physicians will be informed fully, by the AMA, as to the merits and limitations of these two billing procedures. Thus, the phys-

ician can decide for himself in each instance the method of compensation which he prefers. After the regulations have been drawn up, the AMA will advise physicians regarding the options of payment for services available to you.

Certification: Current practices and customary procedures with respect to certification for hospital admission and care should be continued under Public Law 89-97, and the AMA Advisory Committee and the AMA representatives to the technical advisory committees will strive for this objective.

Reasonable fees: The Medicare Law uses such terms as reasonable, usual, and customary fees. Carriers will be advised that these terms will be defined on two bases — the usual or customary fee of the physician rendering the service, and this level of fee in relation to the usual and customary fees of the other physicians in the area who render similar services.

In the event of a dispute between physicians and carriers with respect to reasonable, customary, or usual fees, such disputes should be resolved with the participation of the appropriate local medical society.

Now, as to Puerto Rico. The situation here is entirely different than on the continent. I, myself, would be most presumptuous if I either stated that I completely understood your situation or knew the answers.

Knowing for some time that I would be here to speak to you, I have tried to learn something of Puerto Rico and Puerto Ricans. I find you have a rich and noble heritage. I find all through your history an indomitable spirit to exist through repeated exposures to adversity, a strong determination for individual freedom, a tremendous respect for the dignity of man. I find a successful adaption to North American culture without destruction or abandonment of the fine Spanish culture with which you have been so richly endowed. I see a tremendous accomplishment of development that can be a model for all the world in your operations "Bootstrap." Then, too, I find developed a system of rendition of medical service to the people of Puerto Rico in many ways unlike anything present on the continent. I do not question the necessity of this system particularly at the beginning of "Operation Bootstrap." But I seemed to detect something quite different in this phase of Operation Bootstrap than in other phases such as industry recruitment, housing, agriculture, etc.

In these, the role of government was that of a catalyst. The program was planned as help others so that they may help themselves. Houses were built at minimum cost and of short life, confident that the economics of the householder would improve and he would build a better, more permanent house. Hotels were built, confident that tourists would be attracted which, in turn, would stimulate more hotels being built out of private funds.

Insurance against hurricanes has freed the farmer from unpredictable risks, and has thus encouraged him to farm more and better.

The goal of the program was one of prosperity and a better life in Puerto Rico, by stimulating a dynamic free enterprise system in Puerto Rico. But I do not know the goal of your health care system. Is your present health care system flexible enough so that as the economy of your people improves, they will have available a choice of private care vs. public care? Is a free enterprise system of health care your goal as such seems to be the goal of other aspects of "Operation Bootstrap"? It might well be. I do not know.

Medicare will exert a tremendous impact on your health care system, both title 18 and title 19. Under title 18, as you know, you will have to utilize a carrier or carriers, you will have to provide for deductibles in both hospitalization and medical services, and you will have to provide patient co-insurance in the medical services. These are administrative problems you must, and I am sure can, work out.

Under title 19, the impact could be far greater on Puerto Rico. Title 19 places under Kerr-Mills such already existing programs as aid for dependent children, the blind, the disabled, etc. It increases the amount of federal financial participation in the program and improves many other aspects of the law. But most important it includes under Kerr-Mills hospital and medical care to the needy of all ages by 1967.

Important to Puerto Rico, it removes the ceiling of federal grants heretofore placed on Puerto Rico. This makes it conceivable that Puerto Rico will have available for hospital and medical care for these groups, twice the amount now spent or about 2.5 million dollars, without any increase in expenditures out of the treasury of the Commonwealth. However, to do this you must provide hospital, home and office care for all the needy.

It seems to me that here is an opening for a cooperative program between governmental agencies and private practicing physicians. Greater use, thus, could be made of private facilities and personnel under title 19 than is done at present.

Health care is the joint responsibility of governmental health agencies and private practicing physicians. When either one tries to do it alone or to dominate, quality of care suffers. I would not be talking with the federal government in Washington if I did not thoroughly believe this. I have found in Washington a cordial reception, an attentive ear, a willingness to cooperate and accept ideas and proposals especially when such ideas and proposals are obviously sound and in the best interests of the people whose health both the federal government and the medical profession want to protect.

All these, then, are some of the ways in which Medicare will affect you and your practice. I suspect that many other questions will arise and many problems will present themselves as this new law moves closer to the active stage.

Nevertheless, I do think that this particular period we are all going through must be a time of restraint and prudence. I don't believe that irresponsible anger and frustration will bring us any kind of success.

Even though one small section of the "city" has been occupied, we must remember that our task now is to preserve the remainder of the "city" and to double and redouble our efforts to see that the remaining private sector of medicine is not invaded by the federal government. Let's remember that last year 151,123,000 Americans, or 79% of the population, voluntarily purchased health insurance. This represents a substantial investment by many families to buy care in case of need and certainly must be interpreted as an overwhelming vote of public confidence in the system.

I submit to you that the effects of the medicare law on you and your practice are important. I also submit to you that the effects of expansion of the law and further government intervention and control are even more important to you and your practice.

Thus, we cannot throw in the sponge and quit the struggle. We need your concern

and your influence more than ever before. We need your vigilance. We need your strenght. We need you for the unity of the health profession that these critical times demand. We need your keen desire for freedom in medicine. Without it, together we shall fail in our stewardship to humanity.

James Z. Appel, M.D.

EDITORIAL

PROGRAMA ESPECIAL DE VACUNACION

Se está llevando a cabo con gran éxito un programa especial de vacunación que pretende lograr vacunar en todo Puerto Rico el mayor número posible de niños hasta los cinco años de edad contra polio, difteria, tétano y tosferina, y el mayor número de personas mayores de cinco años de edad contra difteria y tétano.

Desde sus comienzos, esta actividad del Departamento de Salud de Puerto Rico ha recibido el apoyo y la más entusiasta cooperación de la Asociación Médica de Puerto Rico. El impulso que está teniendo este programa ha sido el resultado del "Vaccination Assistance Act", de octubre de 1962, que hizo posible obtener los fondos adicionales necesarios para llevar a cabo una campaña que las autoridades de Salud de Puerto Rico y los dirigentes de la Asociación Médica de Puerto Rico tanto deseaban.

Además de la cooperación de los dirigentes de nuestra Asociación, de las secciones y de los comités que se preocupan por este problema, es necesaria la cooperación absoluta de todos los médicos asociados. Esta cooperación incluye: estimular a nuestros pacientes a que participen en el programa, ayudar en el proceso educativo de individuos y grupos, y estar preparados para contestar las innumerables preguntas que se nos puedan hacer sobre el tema. Estas preguntas tratan de indicaciones, contraindicaciones, reacciones, necesidad de reactivaciones y eficacia de las vacunas. Sobre las indicaciones para la vacunación, no hay duda que toda persona que no haya sido vacunada previamente es un candidato para participar en la campaña. El programa de vacunación especial ha limitado el uso de la vacunación contra la tos ferina hasta los 5 años de edad, por las reacciones más intensas que pueden ocurrir con el antígeno de la tos ferina después de esa edad. El uso de la vacuna Sabin ha sido limitada al mismo grupo, porque esas son las edades de mayor susceptibilidad, y por restricciones en cuanto a los recursos disponibles.

La necesidad de un programa de vacunación en masa en Puerto Rico ha

sido reconocida por las autoridades de Salud y por la Asociación Médica de Puerto Rico, habiendo sido éste el tema de publicaciones previas en el Boletín de la Asociación Médica (1) y de editoriales abogando por la necesidad de tales campañas (2). Una encuesta sobre los niveles de inmunización de menores en Puerto Rico en el 1965, informada por Arbona y Nine-Curt (3) demostró que entre niños menores de 19 años de la Región Noreste de Salud de Puerto Rico, solamente el 40% habían sido inmunizados en algún momento contra viruela y el 46% contra difteria y tétano o contra difteria, tétano y tos ferina. Entre los menores de 11 años, el 50% habían recibido la vacuna Sabin. Llegaron a la conclusión de que menos de la mitad de los niños en la Región Noreste de Puerto Rico tienen inmunidad activa contra enfermedades para las cuales hay vacunas disponibles. Una encuesta previa informada por Martínez en el Boletín (1) demostraba un cuadro mucho peor en cuanto a niveles de inmunización en el 1962. Desde entonces, la situación ha mejorado bastante, principalmente por el gran éxito de la campaña de inmunización con la vacuna Sabin en el 1963. En contraste con los resultados obtenidos contra la poliomielitis, el tétano, según informó Rivera en el 1963 (2), era un problema y sigue siendo un problema en el 1966. Esto se refleja en el trabajo del 1965 de Rodríguez y colaboradores (4), informando una casuística enorme, imposible de recoger si no fuera por el bajo nivel de protección existente en todas las edades en la región sur de Puerto Rico.

La necesidad y las indicaciones para una gran campaña de vacunación están establecidas. El éxito de la misma depende de los recursos disponibles; de la organización, participación y educación de la comunidad y de una actitud positiva y de decidida cooperación por parte de la profesión médica. Debemos reconocer las limitaciones que tienen que afrontar los organizadores de una campaña en masa, aceptar los riesgos mínimos que conlleva vacunar sin un historial clínico y sin examen físico detallado antes de la vacunación y aceptar ciertos riesgos mínimos a cambio de los enormes beneficios derivados de una población inmunizada. El uso de la vacunación a chorro con pistola, aunque hace posible la inoculación sin dolor, produce una incidencia más alta de reacciones locales tales como eritema y nódulos persistentes por varios días después de la vacunación. Esta reacción no debe ser motivo de alarma ni contraindicación para una segunda dosis. En personas que ya han recibido varias dosis previas de toxoide es posible que un exceso de reactivaciones produzca reacciones algo más

intensas, pero las que se han descrito no han sido clasificadas como peligrosas, sino desagradables (5). En el caso de la vacuna oral de Sabin, no se conocen riesgos provenientes de un exceso de dosis de la vacuna. Al contrario, el mayor número de dosis garantiza mejor inmunidad. Personas que hayan recibido la vacuna Salk previamente deben tomar la de Sabin, ya que la Salk requiere una dosis adicional cada 2 años mientras que la Sabin probablemente confiere inmunidad permanente después de 2 ó 3 dosis (6).

En relación con el intervalo entre una inmunización y otra existe una creencia generalizada de que si se prolonga grandemente, se pierde la efectividad de la primera dosis y es necesario repetir un curso completo de inmunizaciones para poder lograr inmunidad. La evidencia disponible indica lo contrario. Una prolongación razonable del período entre una dosis y otra aumenta la probabilidad de mejores títulos de anticuerpos cuando se da la segunda dosis. No se conoce con certeza hasta qué límite puede llegar esta afirmación, pero dando como ejemplo el caso del tétano, se ha comprobado que una persona que ha recibido una serie inicial de dos inmunizaciones de tétano puede producir excelentes niveles de anticuerpos en un término de 24 horas con otra dosis aplicada hasta 18 años más tarde (5).

El plan para la campaña de inmunizaciones que se está llevando a cabo actualmente es repetir las mismas dosis dentro de un período de alrededor de 6 meses después de la dosis inicial. En esta segunda fase será aún más necesaria la cooperación de todos los médicos de Puerto Rico. En muchas ocasiones, tanto en la práctica privada como en campañas de vacunación en masa, se aplaza la vacunación por motivo de infecciones respiratorias leves o de manifestaciones alérgicas respiratorias crónicas. En muchos casos llega un lactante a la edad de un año sin haber recibido una sola dosis de vacuna alguna. Es importante recordar que el peligro de una enfermedad como la tos ferina en esta edad es inmensamente mayor que el pequeño riesgo de vacunar estos niños, aún cuando tengan ligeros síntomas respiratorios. La alta mortalidad y el daño pulmonar permanente producidos por la tos ferina en los lactantes son bien conocidos de todos. En cuanto a la vacunación de personas alérgicas, es probable que éstas sean, precisamente, las que más necesitan estar protegidas contra difteria y tétano, ya que son las que probablemente tendrían reacciones graves si fuera necesario el uso de la antitoxina elaborada de suero de caballo.

Las complicaciones que deben mantener al médico en guardia son, hiperpi-

rexia o convulsiones producidas por la dosis inicial. Esto es más importante en el niño pre-escolar vacunado con la DPT, ya que el riesgo principal es por el antígeno de la tos ferina. En estos casos puede continuarse la vacunación en dosis fraccionadas o usando los antígenos de difteria y tétano solamente.

La campaña de vacunación no ha incluído la vacuna de viruela ni la de sarampión. La vacunación contra viruela podría demorar la campaña, ya que requeriría un interrogatorio detallado que incluiría datos sobre erupciones, tanto en el paciente como en los que conviven con él. Igualmente, la incidencia mayor de reacciones a la vacunación contra viruela (7) podría ahuyentar a un número de personas que por ahora está cooperando plenamente con el programa. La vacunación contra sarampión es una que de no ser por su alto costo, debiera estarse usando en masa en todo niño a la edad de un año. El sarampión es una enfermedad cuyo peligro no ha sido reconocido debidamente. Está seguida de una alta incidencia de complicaciones tales como bronconeumonía y otitis media, que en muchos casos, y particularmente en niños desnutridos, evolucionan hacia un desenlace fatal. Estas muertes se informan como bronconeumonía y no como debidas a sarampión. Otra complicación importante es la encefalitis, con sus correspondientes secuelas. Encefalitis por sarampión se ha estimado que ocurre en 1 de cada 1000 casos de sarampión. La vacuna de virus vivo de sarampión es altamente efectiva y probablemente la inmunidad producida es permanente (8). Las contraindicaciones más importantes son, embarazo, tratamiento con corticoesteroides y alergia al huevo. Un inconveniente adicional es que la vacuna idealmente debe estar precedida por una prueba de tuberculina (9). Si ésta es positiva, debe tratarse al paciente con isoniacida por un período de tres meses después de aplicada la vacuna o de un año completo si se trata de un niño menor de 5 años de edad. Este llamado inconveniente presenta claramente una oportunidad de combinar una campaña de vacunación contra sarampión con la campaña existente actualmente para la prevención y búsqueda de casos de tuberculosis. Un infante con tuberculina positiva apunta a un adulto tuberculoso que probablemente convive con él. El examen de todos los contactos de este niño permitiría descubrir y tratar a tiempo al enfermo fuente de contagio. Además, proveería la oportunidad de administrarles quimioprofilaxis a los contactos y a otros niños infectados. El gobierno federal está consciente de la importancia de la prueba de la tuberculina y de la vacunación contra sarampión, de manera que es casi seguro que haya fondos para ambos propósitos en un futuro cercano.

Aprovechando estos fondos, el Departamento de Salud podría fácilmente añadir este nuevo programa a su lista de éxitos en campañas de medicina preventiva.

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RESUCITACION CAROIOPULMONAR

PRINCIPIOS PRACTICA ENSEÑANZA

¿PODRIA USTED RESUCITAR A UNA PERSONA? SI

¿DISPONE USTED DE UN PLAN DE ACCION EFICIENTE? ?

HAY EVIDENCIA DE QUE MUCHAS DE LAS MUERTES QUE OCURREN ANUALMENTE PODRIAN HABERSE EVITADO UTILIZANDO A TIEMPO LAS TECNICAS MODERNAS DE RESUCITACION SON MUCHAS LAS VICTIMAS DE ATAQUES CARDIACOS (FIBRILACION VENTRICULAR SIN INFARTO SEVERO) QUE ESTAN DISFRUTANDO DE "UNA SEGUNDA OPORTUNIDAD" EN LA VIDA GRACIAS A UNA PRONTA Y EFICIENTE PRIMERA AYUDA EN 1958 SE ACEPTO LA RESPIRACION BOCA A BOCA COMO LA MAS VALIDSA FORMA DE RESPIRACION ARTIFICIAL EN 1960 SE RECOMENDO EL MASAJE CARDIACO EXTERNO PARA EL TRATAMIENTO DE PARO CARDIACO. FUE ENTONCES QUE SURGIERON LOS PROGRAMAS DE ENTRENAMIENTO EN LAS TECNICAS DE RESUCITACION PARA MEDICOS, PERSONAL PARAMEDICO Y PUBLICO TODAVIA HAY MUCHOS MEDICOS QUE NO HAN TENIDO LA OPORTUNIDAD DE PRACTICAR LOS NUEVOS METODOS DE RESUCITACION TODO MEDICO DEBE BUSCAR LA OPORTUNIDAD DE ADQUIRIR CONOCIMIENTOS Y EXPERIENCIA EN LAS TECNICAS MODERNAS DE RESUCITACION

HE AQUI SU OPORTUNIDAD

¡Aprovechela!



DEPARTAMENTO ANESTESIOLOGIA
HOSPITAL del MAESTRO

M A COLON MORALES M D.
A DE LA CRUZ M D
VICTOR GONZALEZ M.D.

PRIMERA AYUDA



OBJETIVO RE OXIGENAR EL SISTEMA CENTRAL NERVIOSO

1- PROVEER VIA DE AIRE LIBRE
HIPER EXTENSION DE LA CABEZA Y / O ELEVAR MANDIBULA
REMOVER CUERPO EXTRAÑO

2- RESPIRACION ARTIFICIAL
BOCA A BOCA (O VARIANTE)

3- CIRCULACION ARTIFICIAL
COMPRESION EXTERNA DEL CORAZON



NO REQUIEREN EQUIPO - PUEDEN INICIARSE EN CUALQUIER MOMENTO.
DEBEN UTILIZARSE EN FORMA EFICIENTE.



TRATAMIENTO DEFINITIVO

OBJETIVO RE INICIAR CIRCULACION ADECUADA Y ESPONTANEA

1- DIAGNOSTICO - ECG - ASISTOLIA - FIBRILACION VENTRICULAR

2- MEDICACION

- EPINEFRINA (1:10,000) I V O INTRA CARDIACA - CARDIOTONICO, VASO PRESOR
- CACL 0 GLUCONATO CALCIO I V O INTRA CARDIACO - CARDIOTONICO
- BICARBONATO DE SODIO
  0 75 Gm en 50 cc I V
  CONTRARRESTA ACIDOSIS
  MEJORA CIRCULACION CEREBRAL
- LEVOPROPE, NEODIMEFRINA - VASOPRESORES
- QUINIDINA, PROCAINAMIDA, 100 mg PRN - DISMINUIR IRRITABILIDAD MIOCARDIO

3- DEFIBRILACION
EXTERNA
CORRIENTE ALTERNA 400 to 600 VOLTIOS
CORRIENTE DIRECTA 100 - 600 WATTS SEGUNDOS



REPITA MEDICACION Y DEFIBRILACION MIENTRAS SEA NECESARIO

RESUCITACION CARDIOPULMONAR DEBE SER CONTINUADA Y SIN INTERRUPCION
HASTA QUE LA RESPIRACION Y CIRCULACION SEAN ESPONTANEAS Y ADECUADAS



NOTICIAS

Locales

BOLETINES VIEJOS

La Asociación Médica de Puerto Rico está interesada en obtener copia de los siguientes números del Boletín:

Año	*Meses*
1920	enero a diciembre
1922	enero a diciembre
1923	enero a diciembre
1925	enero a diciembre
1927	enero a diciembre
1928	enero a diciembre
1942	enero a diciembre
1943	enero a diciembre
1944	enero a diciembre
1953	abril, junio y agosto
1957	agosto
1962	julio

Aquellos miembros de nuestra matrícula que tengan estos volúmenes y deseen donárselos a la Asociación Médica, favor de comunicarse con el Sr. Eulogio Bermúdez Vélez, Secretario de Redacción.

CONGRESO NACIONAL DE ETICA MEDICA Y PROFESIONALISMO

El Dr. Luis Sala, Presidente de la Asociación Médica de Puerto Rico, ha designado al Dr. Carlos Quilichini, quien Preside el Comité de Etica de la Asociación Médica de Puerto Rico para que represente a nuestra Asociación en el Congreso Nacional de Etica Médica y Profesionalismo que auspicia la Asociación Médica Americana. Dicha actividad se celebrará en la ciudad de Chicago en marzo de 1966.

OPORTUNIDADES DE TRABAJO PARA MEDICOS

1. Hemos recibido notificación del Fuerte Brooke en San Juan expresando la disponibilidad de oportunidades de trabajo para médicos en la oficina de exámenes de las Fuerzas Armadas en el Fuerte Brooke, San Juan. Para información adicional se puede llamar al Capitán P. J. Alamo, teléfono 722-4000, extensión 3280. Fuerte Brooke.

2. El Sr. Tomás E. Alcalá Gómez, Director de la División de Corrección del Departamento de Justicia, nos informa que la Administración de Instituciones Penales tiene un puesto vacante de Médico 5. Director Médico, en la Penitenciaría Estatal. Los interesados pueden comunicarse con el Sr. Alcalá Gómez en el Departamento de Justicia.

3. La Phillips Petroleum Co. solicita médicos consultores para hacer exámenes físicos a los candidatos para empleo en la compañía. Dichos consultores serán necesarios para exámenes médicos especiales a los empleados y para manejar cualquier enfermedad o accidente relacionados con el trabajo.

Aquellos interesados deberán comunicarse con:

Hiram Vázquez Milán, M.D.
Comisión Industrial de P. R.
Apartado 3905
San Juan, Puerto Rico

DE INTERES PARA LOS ORTOPEDAS

La Association of Bone and Joint Surgery celebrará su convención anual del 13 al 17 de abril de 1966 en el Hotel Americana, San Juan, Puerto Rico.

La Piedmont Orthopedic Society celebrará su convención anual del 5 al 8 de mayo de 1966 en el hotel Dorado Beach.

Para más detalles sobre conferenciantes, participantes, programa, etc., favor de comunicarse con el Dr. Arturo Cadilla, Jr., en Bayamón.

ASOCIACION GENERAL ANTITUBERCULOSA DE P. R.

Los beneficios que derivará el paciente de tuberculosis en Puerto Rico del programa de MEDICARE y de otros programas federales de reciente creación, será el tema central de la Asamblea Anual de 1966 a celebrarse en abril 29 y 30 en el Hotel San Jerónimo.

La presentación de este tema será por medio

de un panel en el cual participarán las personas que están a cargo de estos programas en Puerto Rico, con discusión abierta por los asistentes.

Otros temas a discutirse en la Asamblea serán "Introducción a las Enfermedades Respiratorias no tuberculosas;" "Mis experiencias en un Programa de Tuberculina," por estudiantes de la Universidad Inter Americana y una película sobre "Los Efectos del Cigarrillo en la Salud".

También habrá sesión administrativa y los acostumbrados actos sociales.

Todos están invitados a reservar la fecha, abril 29 y 30 para asistir a tan importante asamblea.

PRIMER CONGRESO DE MEDICINA FISICA Y REHABILITACION

El Primer Congreso de Medicina Física y Rehabilitación, se celebrará en Puerto Rico de abril 25 al 29 de 1966.

El grupo de artritis vendrá de la Clínica Mayo bajo la dirección del Dr. Earl Elkins. El panel sobre la hemiplegia de la Universidad de Nueva York, presidido por el Dr. Howard Rusk; el de los amputados viene de la Universidad de California y será dirigido por el Dr. Charles Bechtol. El seminario sobre electrodiagnosis será presidido por el Dr. W. T. Liberson de Chicago y el Dr. C. B. Wynn Parry de Londres.

Las mañanas serán dedicadas a conferencias por distintas autoridades sobre el tema del día, y las tardes a repaso y discusión sobre pacientes en un centro de rehabilitación.

Además, el grupo de California ofrecerá un pequeño curso sobre Prostesis durante la segunda semana, o sea del 2 al 6 de mayo, 1966, en el Centro de Rehabilitación del Departamento de Rehabilitación Vocacional.

La Universidad de California otorgará un certificado de asistencia a todas las personas que hayan asistido fielmente a este cursillo.

LECTURES ON BASIC SCIENCE APPLICATIONS TO CLINICAL MEDICINE

The following series of lectures will be given at the Medical Service Conference Room, Veterans Administration Hospital, San Juan, Puerto Rico. 11:00 a.m. on Tuesdays.

Physicians and students are invited to attend.

April 5 Ideas on the Pathogenesis of Ischemic Heart Disease — Dr. Angel A. Colón.

April 12 The Problem of Health in Puerto Rico as Seen by a Parasitologist — Dr. José F. Maldonado

April 19 The Diagnosis of Intestinal Parasites — Dr. José F. Maldonado

April 26 Reconstituted Cell Membranes as Transducers for the Electrical Detection of Antigen-Antibody and Enzyme-Substrate Reactions. — Dr. José del Castillo

May 3 Clinical and Pathologic Variants of S.L.E. — Dr. Russell A. Del Toro

May 10 The Diagnosis of Rheumatoid Disease — Dr. Russell A. Del Toro

May 17 Immunoglobulins and Nuclear Antibodies — Dra. Esther González de Rodríguez.

May 24 Estudios sobre la Trombocitopenia y Trombocitopatías — Dr. A. A. Cintrón-Rivera

May 31 Physiological Basis for Clinical Organ Scanning — Dr. A. L. Rodríguez Rosado

June 7 Newer Viruses Pathogenic for Man — Dr. Rafel Mariñelarena

June 14 Viruses and Neoplastic Disease — Dr. Rafael Mariñelarena

June 21 Recent Advances in the Search for Antiviral Substances — Dr. Rafael Mariñelarena

Estudio sobre Cáncer

El Dr. Isidro Martínez, Director del Registro Central del Cáncer del Departamento de Salud ha recibido un donativo del Instituto Nacional del Cáncer para llevar a cabo un estudio epidemiológico de todos los casos de cáncer del esófago, faringe y cavidad bucal diagnosticados en Puerto Rico durante el año 1966.

Muchos de estos casos son atendidos en hospitales privados y por sus médicos privados. El doctor Martínez solicita la cooperación de todos los médicos autorizando a los entrevistadores que le asisten en este estudio a acercarse a los pacientes.

Abril 24-29, 1966 — Primer Congreso de Medicina Física y Rehabilitación del Caribe, Hotel San Juan, San Juan, P. R.

CONGRESO MUNDIAL DE MEDICINA DEL DEPORTE

El Comité Olímpico de Puerto Rico a través de su Presidente, el Sr. Felicio M. Torregrosa, nos informa sobre la celebración del XVI Congreso Mundial de Medicina del Deporte que se celebrará en Hannover, Alemania Occidental, durante los días 12 al 16 de junio de 1966. Cual-

quier interesado puede obtener mayor información comunicándose con las oficinas centrales de la Asociación Médica de Puerto Rico.

PREMIOS DOME LABORATORIES

Dome Laboratories anteriormente Dome Chemicals, Inc., de Nueva York ha establecido por intermedio del Colegio Ibero Latinoamericano de Dermatología (CILAD), dos premios de 800 dólares el primero y 400 dólares el segundo para los mejores trabajos originales de investigación no publicados previamente y relativos a algún aspecto fundamental de la dermatología. Se otorgará además diploma y medalla a todos los firmantes de los trabajos premiados.

Los trabajos deben ser escritos en Idioma Español o Portugués.

Los trabajos para optar al premio deben ser presentados al VI Congreso Ibero Latinoamericano de Dermatología.

Este primer concurso se cerrará el 31 de octubre de 1966.

Para informes más detallados sobre las condiciones del concurso, favor escribir a:

Dr David Grinspan

Arenales 947 - 2o. A Buenos Aires, Argentina

DISTRICT POISON CONTROL CENTERS

The following have been designated District Poison Control Centers of Puerto Rico.

1. San Juan Municipal Hospital
   Dr. Oswaldo González Alvarez, Director
   Tel. 724-7002
   Centro Médico, Río Piedras
2. Ponce District Hospital
   Dr. Luis A. Rosario, Director
   Emergency Room
   Tels: 842-2080; 842-2048
3. Arecibo District Hospital
   Dr. Jesús Rodríguez García, Director
   Tel. 878-3535, Ext. 31
4. Fajardo District Hospital
   Dr. Rubén Ramón, Director
   Tel. Nº 566
5. Aguadilla District Hospital
   Dr. Herminio Aluarel, Director
   Tel. 791-0200
   Dr. Pedro Mendoza, Asst. Director
   Tel. 791-0200
   Aguadilla District Hospital
   Dr. Sidney Kaye
   Professor of Toxicology and
   Legal-Medicine
   Coordinator for The Health Department
   Institute of Legal-Medicine
   Escuela de Medicina, U.P.R.
   Tel. 765-0615; 765-4880, Centro Médico
   Río Piedras, P.R.

Nacionales

COURSE IN LARYNGOLOGY AND BRONCHOESOPHALOGY

March 21 to April 2, 1966. The Department of Otolaryngology of the Illinois Eye and Ear Infirmary and the College of Medicine of the University of Illinois at Medical Center, Chicago, will conducts a postgraduate course in Laryngology and Bronchoesophagology. This course is limited to fifteen physicians and will be under the direction of Paul H. Holinger, M.D. It will be held largely at the new Illinois Eye and Ear Infirmary, 1855 West Taylor Street, Chicago, and will include visits to a number of Chicago hospitals. Instruction will be provided by means of animal demonstrations and practice in bronchoscopy and esophagoscopy, diagnostic and surgical clinics, as well as didactic lectures.

Interested registrants will please write directly to the Department of Otolaryngology, College of Medicine of the University of Illinois at the Medical Center, Postoffice Box 6998, Chicago, Illinois 60680.

AMERICAN COLLEGE OF PHYSICIANS POST GRADUATE COURSES

Mar. 28 - April 1. *Basic Mechanisms in Internal Medicine,* University of Toronto, Toronto, Ontario, Canada; K. J. R. Wighaman, M.D., F.A.C.P., Director.

April 14-16. *Current Concepts of Renal, Gastrointestinal and Circulation Physiology,* co-sponsored by the American Physological Society, Barbizon-Plaza Hotel, New York, N.Y.; Daniel H. Simmons, M.D., F.A.C.P., and Charles Kleeman, M.D., F.A.C.P., Co-Directors.

May 9-13. *Internal Medicine in Light of Recent Developments,* Pennsylvania Hospital, Philadelphia, Pa.; Garfield G. Duncan, M.D.; F.A.C.P., and Robert J. Gill, M.D., F.A.C.P., Co-Directors.

May 16-20, *Physiological Aspects of Cardiopulmonary Disease,* Indiana Univ., Indianapolis,

Ind.; John B. Hickman, M.D., F.A.C.P., Director:

May 23-25. *National Tuberculosis Association.* The 1966 Annual Meeting of the American Thoracic Association will be held in San Francisco, California.

June 13-17. *Advanced Psychiatry for Internists,* Baltimore Psychoanalytic Institute, Baltimore, Md.; Ephraim T. Lisansky, M.D., F.A.C.P., Director.

June 15-18. *Neurology for the Internist,* Bowman Gray School of Medicine, Winston-Salem, N.C.; James F. Toole, M.D., F.A.C.P., Director.

AMERICAN INDUSTRIAL HEALTH CONFERENCE

April 25-28. The 1966 American Industrial Health Conference, will be held in Detroit, Michigan, with headquarters at the Sheraton Cadillac Hotel and meetings in Cobo Hall, it has been announced by the *Industrial Medical Association and the American Association of Industrial Nurses.* This medical-nursing Conference which is comprised of the annual meetings of the two sponsoring Associations, will bring together approximately 2,000 persons which, in addition to industrial physicians and nurses, will include industrial hygienists, safety engineers, public health officials, military service medical personnel, university faculty members, management representatives and others who have an interests in the health of the working population. The annual meeting of the Industrial Medical Association will mark the organization's 50th anniversary meeting.

The scientific program, in which many of the nation's experts in the field of occupational health will participate, will be augmented by both scientific and technical exhibits. Intensive courses in selected areas of medical practice also will be presented. Further information about the Conference may be obtained by writing American Industrial Health Conference, 55 East Washington Street, Chicago, Illinois 60602.

LEDERLE RESIDENCY SUPPLEMENTS

The American Geriatrics Society today announced the renewal of three $1800 grants to encourage resident physicians to devote more time to the study of the medical problems of the aging.

The grants will supplement the salaries paid to resident physicians while they continue their medical education, and are made possible by Lederle Laboratories, a Division of American Cyanamid Company.

The Lederle Residency Supplements will cover the period between July 1966 to June 1967. They were inaugurated in 1962.

Application for the grants should be addressed to the Chairman, Fellowship Committee, American Geriatrics Society, 10 Columbus Circle, New York, N. Y. 10019. Deadline for applications is June 1, 1966. Announcement of the awardees will be made at the AGS annual meeting June 23-24 at Chicago.

1966 NORMAN A. WELCH, M.D. ESSAY CONTEST ON MEDICAL ETHICS

The American Medical Association, through its Judicial Council, will sponsor a Medical Ethics Essay Contest, open during this academic year to junior and senior students in accredited medical schools in the United States.

The contest, to be known as the Norman A. Welch, M.D. Essay Contest, is another step in the Judicial Council's Expanded Program on Medical Ethics, according to the joint announcement by F. J. L. Blasingame, M.D., AMA's Executive Vice President, and James H. Berge, M.D., Chairman of the Judicial Council.

Cash prizes totaling $1,000, made possible by a special appropriation by the AMA's Board of Trustees, will be awarded to the winning essays. First prize will be $500, second prize $300, and third prize $200.

The contest is being named in honor of the late Norman A. Welch, M.D., a leading figure in American medicine for many years, who died September 3, 1964, while serving as the 118th President of the AMA.

Complete contest rules, as well as suggested essay topics, are available upon written request from the Department of Medical Ethics, American Medical Association, 535 N. Dearborn Street, Chicago, Illinois 60610. They also may be obtained at the offices of the medical school deans.

June 1, 1966, has been set as the deadline for entries in the contest, which the Judicial Council hopes will be continued on an annual basis. Awards in the 1965-66 contest will be announced at the AMA Clinical Convention, in November, 1966.

Judging of the contest will be by a Medical Ethics Essay Contest Committee, composed of prominent physicians, and by members of the Judicial Council.

Se solicita Médico que desee o necesite vivir en Nueva York para hacerse cargo de práctica en oficina con promedio de entrada de más de $50,000 anuales los últimos 15 años. Debe ser Ginecólogo y preferiblemente Cirujano en General.

El interesado puede comunicarse con:

Dr. M. Janer
697 West End Avenue,
New York, New York

CARDIOLOGY NINE MONTH TUTORIAL PROGRAM

A nine month tutorial program in *Cardiology*, September 15, 1966 to June 15, 1967, will be offered by the Institute for Cardiopulmonary Diseases, Scripps Clinic and Research Foundation, La Jolla, California. This will be an intensive academic effort covering the field of cardiovascular diseases and is especially designed for the physician, U.S.A. or abroad, who wants an intensive orientation in cardiology. The objective will be to offer training in the broad discipline of academic cardiology: the techniques of teaching, the use of the literature, the preparation of a manuscript, the art of consultation, history taking, the methods of the specialty (auscultation, x-ray, fluoroscopy, electro and vectorcardiography, phonocardiography, cardiac catheterization, angiography, pulmonary function studies), the care and use of experimental animals, an introduction to biophysics and statistics, the selection and maintenance of equipment, maintenance of files and records.

TUITION $1,000

For Information, Write:

Executive Secretary, Institute for Cardio Pulmonary Diseases Scripps Clinic and Research Foundation La Jolla, California

(A FORMAL PROGRAM OF THE AMERICAN COLLEGE OF CARDIOLOGY)

BIOCHEMICAL COMMUNICATION

The New York Academy of Sciences and the Public Health Service Audiovisual Facility will cosponsor a conference on "Biomedical Communication: Problems and Resources" at The Waldorf-Astoria Hotel in New York City, April 4, 5, and 6, 1966.

The conference will present practical ways in which communications media, personnel, and systems can help achieve important health objectives, with full recognition of the need for conserving monetary and human resources. Those in attendance will include deans of medical schools and other schools of the health professions, hospital administrators, representatives of organizations with health interest, and members of the Academy.

According to Dr. James Lieberman, Director of the Public Health Service Audiovisual Facility and Conference Chairman, "The conference will have broad and significant implications for the biomedical community at large." "Further," he added, "in the field of medicine and the allied sciences, as in few others, man's discovery of knowledge far exceeds his efforts to communicate and apply that knowledge."

The program will emphasize resources available for solving communication problems arising from a shortage of faculty, and from the growing body of biomedical knowledge and curriculum content which is expanding at an unprecedented rate. Inquiries may be directed to Public Health Service Audiovisual Facility, Atlanta, Georgia 30333. Attention: BIOMEDCOM

Internacionales

CURSO COMPLETO DE GASTROENTEROLOGIA PARA GRADUADOS

A partir del 4 de marzo de 1966, se encontrará abierta la inscripción en el Departamento de Graduados de la Facultad de Ciencias Médicas de la Universidad Nacional de Buenos Aires, Paraguay 2155, para el Curso Completo de Gastroenterología que dictará en el Hospital Nacional de Gastroenterología "*Dr. Bonorino Udaondo*" el Docente autorizado de Cirugía, Dr. Marcos Maur, con la colaboración de los siguientes Especialistas del mencionado Establecimiento: Dres. Manuel M. Ramos Mejía, Adolfo M. Rey, Victorino D' Alotto, Manuel Lemos García, Adolfo Schapira, Alfonso Fraise, Solomón Krigpún, Julio C. Rojas, Pedro Scorza, Leonardo Braier, Jorge Caffarello, Horacio Capizzano, Aldo Copello, Erman Crosetti, Emilio Chattás, Fernando Galindo, Atilio Iorio, Ricardo A. Sabagh, Isaías Schor, Ramón Pando, Raúl Rodríguez, Alberto Apud, Ricardo de Elizalde, León Kesner, Antonio Musi, Gustavo A. Schickendantz., Ricardo Vivone y Luciano Bombaci. Actuará de Encargado Suplente del Curso el Docente autorizado de Cirugía Dr. Pedro Cotella.

El Curso tendrá una duración de 8 meses, desde

el 4 de abril al 5 de diciembre. Los médicos inscriptos deberán concurrir todos los días hábiles de 7:30 a 12 horas, pudiendo inscribirse egresados de hasta cinco años. Para médicos residentes en otros países, no hay límite de antigüedad pero deben traer en el momento de inscripción, el título de médico o bien copia autenticada del mismo.

Está Previsto el Siguiente Programa Teórico:

Clases Magistrales los días lunes y viernes a las 11 horas, sobre distintos aspectos de Fisiopatología Gastroenterológica abarcando toda la Patología Digestiva. Aprendizaje de los distintos medios complementarios de diagnóstico: Radiología, Endoscopía, Laboratorio, Clases de Dietología vinculadas a Patología Digestiva, Clases de Medicina Psicosomática en relación con la Gastroenterología.

Ateneos de: Radiología, Anatomía Patológica, Clínico-Quirúrgico y Bibliográfico así como un cursillo de Cirugía Experimental. Para las Clases Prácticas, que también tendrán desarrollo todos los días de 7:30 a 11 horas, se constituirán seis comisiones que rotarán por los siguientes Servicios: Clínica, Nutrición, Laboratorio de Investigaciones, Radiología, Endoscopía, y Proctología.

Los inscritos cirujanos, además de realizar instrucción en los Servicios indicados en el párrafo precedente, realizarán ejercicios de Cirujía Experimental y los tres últimos meses se adscribirán al Servicio de Cirujía del Establecimiento, donde actuarán en el mismo plano que los médicos becarios con que cuenta el Hospital.

El Departamento de Graduados de la Facultad otorgará certificación a los inscritos que hayan cumplido con el 80% de las actividades previstas. Para información complementaria dirigir carta al Director del Curso, Avenida Caseros 2061, Buenos Aires, Argentina, o bien personalmente a la Biblioteca del Hospital, tercer piso, teléfono Nº 27-4641.

Agosto 20-25, 1966 *Noveno Congreso Internacional de Enfermedades del Tórax.*

PAN-PACIFIC SURGICAL ASSOCIATION TENTH CONGRESS

The Board of Trustees of the Pan-Pacific Surgical Association announces the dates of the Tenth Congress in Honolulu and the Second Mobile Educational Seminars which travels to countries bordering the Pacific basin.

Part I, the Honolulu portion of the Congress, will convene at the Princess Kaiulani Hotel on September 20, 1966, and continue through September 28.

Part II and III will depart Hawaii on September 28 and travel to Japan and Hong Kong with Part II returning to San Francisco on October 10, in time for the opening of the American College of Surgeons, and Part III continuing on to the Philippines, Thailand, India, Singapore, Australia and New Zealand, returning to Hawaii on November 1, 1966.

The Tenth Congress offers an extensive scientific program presented by more than 450 leading surgeons from the United States and 22 other countries in 12 different specialties: Colon and Anorectal Surgery, General Surgery, Neurosurgery, Obstetrics and Gynecology, Ophthalmology, Otolaryngology, Orthopedics, Plastic Surgery, Thoracic-Cardiovascular Surgery, Urology, Anesthesiology and Radiology. All physicians and surgeons are invited to attend these meetings.

In this space age, diseases are no longer confined to geographical boundaries and it has become essential for the medical profession everywhere, to share its scientific knowledge and efforts. Therefore, Pan-Pacific with its Mobile Seminars, is expanding its activities in teaching, education and dissemination of knowledge to doctors living in the Pacific rim countries who are unable to participate in the Honolulu portion of the Scientific Congresses, in exchange for further education and skill in the diseases unique to the Pacific areas. The Pan-Pacific Surgical Association believes, through the vehicle or medium of medicine and surgery, that our greatest contribution to peace and harmony among all men of all nations can be realized.

For further information, please write: Pan-Pacific Surgical Association, Room 236, Alexander Young Building, Honolulu, Hawaii 96813.

Oct. 23-20, 1966 IV International Cancer Congress, Tokyo, Japan. A charter flight and several group flights are contemplated, thus substantially reducing the cost of transportation. Members of the immediate family of congress participants will be eligible. Anyone interested should communicate with Hirsch Marks, M.D., 135 East 57th Street, New York 22, N.Y.

REVISTA DE LIBROS

HELMINTIASIS DEL HOMBRE EN AMERICA: *Por José F. Maldonado, Cátedra de Zoología Médica, Escuela de Medicina, Universidad de Puerto Rico — 28 y 529 pgs. con 263 figuras, Editorial Científico Médico, Barcelona, España.*

En su libro Helmintiasis del Hombre en América, el Profesor Maldonado cubre a cabalidad la parte de parasitología sobre los helmintos relacionados al hombre, en especial los vermes más comunes en América y que deben ser mejor conocidos por representar problemas de salud, especialmente en áreas subdesarrolladas. El libro está escrito en un lenguaje claro y sencillo, propio de un buen maestro que ha dedicado muchos años a la enseñanza de estudiantes de tecnología médica, medicina y salud pública. Permea el libro la vasta experiencia del autor, que además ha documentado el contenido con una enorme cantidad de citas bibliográficas.

El material se presenta en cuatro divisiones mayores: Nemátodos, Tremátodos, Cestodos y Técnicas Parasitológicas. En las primeras tres, luego de una introducción general al grupo, discute los vermes individualmente, incluyendo morfología, biología, clínica, diagnóstico, tratamiento, epidemiología y prevención. Incluye una acertada exposición de los problemas actuales que nos confrontamos en el control de la enfermedad. La sección sobre Técnicas Parasitológicas expone en forma clara y ordenada los distintos métodos de uso más común. Su exposición destila la enorme experiencia del autor en estos procedimientos.

Las citas bibliográficas son extensas y al día. Debido a su gran número, el autor opta por ofrecer únicamente las iniciales de las revistas para ahorrar espacio. Estas citas bibliográficas han sido bien seleccionadas y son de gran utilidad para las personas que desean aumentar sus conocimientos en la materia. Las abundantes ilustraciones en el libro tienen una excelente resolución de detalles que muestran la meticulosa selección e impresión de las fotografías y grabados. Se echa de menos un índice al final sobre los tópicos del contenido.

Esta obra se recomienda para estudiantes y médicos. Debe ser leída por todos y formar parte de su biblioteca profesional.

Francisco Ramos — Morales, M.D.

Instrucciones para los Autores:

El Boletín acepta para su publicación artículos relativos a medicina y cirugía y las ciencias afines. Igualmente acepta artículos especiales y correspondencia que pudiera ser de interés general para la profesión médica.

El artículo, si se aceptara, será con la condición de que se publicará únicamente en esta revista.

Para facilitar la labor de revisión de la Junta Editora y del impresor, se requiere de los autores que sigan las siguientes instrucciones:

a) Los trabajos deberán estar escritos a máquina a doble espacio y por un solo lado de cada página, en duplicado y con amplio margen.

b) En página separada debe incluirse lo siguiente: título (no excediendo de 80 letras y espacios), nombre del autor (es), institución y dirección postal del autor.

c) Artículos referentes a resultados de estudios clínicos o investigaciones de laboratorio deben organizarse bajo los siguientes encabezamientos: (1) introducción, (2) material y métodos, (3) resultados, (4) discusión, (5) resumen (en español e inglés), y (6) referencias.

d) Artículos referentes a estudios de casos aislados deben organizarse en la siguiente forma: (1) introducción, (2) observaciones del caso, (3) discusión, (4) resumen (en español e inglés), (5) referencias.

e) Las tablas, notas al calce y leyendas deben aparecer en hojas separadas.

f) Si un artículo ha sido leído en alguna reunión o congreso, así debe hacerse constar como una nota al calce.

g) Deben usarse los nombres genéricos de los medicamentos. Podrán usarse también los nombres comerciales, entre paréntesis, si así se desea.

h) Se usará con preferencia el sistema métrico de pesos y medidas.

i) Las fotografías y microfotografías se someterán como copias en papel de lustre sin montar. Los dibujos y gráficas deben prepararse a tinta negra y en papel blanco. Todas las ilustraciones deben estar numeradas (números arábigos) e indicar la parte superior de las mismas. Debe escribirse una leyenda para cada ilustración.

j) Las referencias deben ser numeradas sucesivamente de acuerdo con su aparición en el texto. Los siguientes ejemplos pueden servir de modelo:

6. *Koppisch, E.* Pathology of arteriosclerosis. Bol. Asoc. Med. P. Rico 46: 505, 1954. (artículo de revista).
4. *Wintrobe, M. M.* Clinical Hematology, 3rd Ed. Lea and Febiger, Philadelphia, 1952, p. 67. (libro).

Deben usarse solamente las abreviaturas indicadas en el Cumulative Index Medicus que publica la Asociación Médica Americana.

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The Boletín will accept for publication contributions relating to the various areas of medicine surgery and allied medical sciences. Special articles and correspondence on subjects of general interest to physicians will also be accepted. All material is accepted with the understanding that it is to be published solely in this journal.

In order to facilitate review of the article by the Editorial Board and the work of the printer, the authors must conform with the following instructions:

a) The entire manuscript, including legends and references, should be typewritten double-spaced in duplicate with ample margins.

b) A separate title page should include the following: title (not to exceed 80 characters and spaces), author's name (s); institution, and author's mailing address.

c) Articles reporting the results of clinical studies or laboratory investigation should be

organized under the following headings: (1) introduction, (2) material and methods, (3) results, (4) discussion, (5) summary in English and Spanish, (6) references.

d) Case reports will include (1) introduction, (2) description of the case, (3) discussion, (4) summary in English and Spanish, (5) references.

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f) If the paper has been presented at a meeting, the place and date should be stated as a footnote.

g) Generic names of drugs should be used. Trade names may also be given in parenthesis, if desired.

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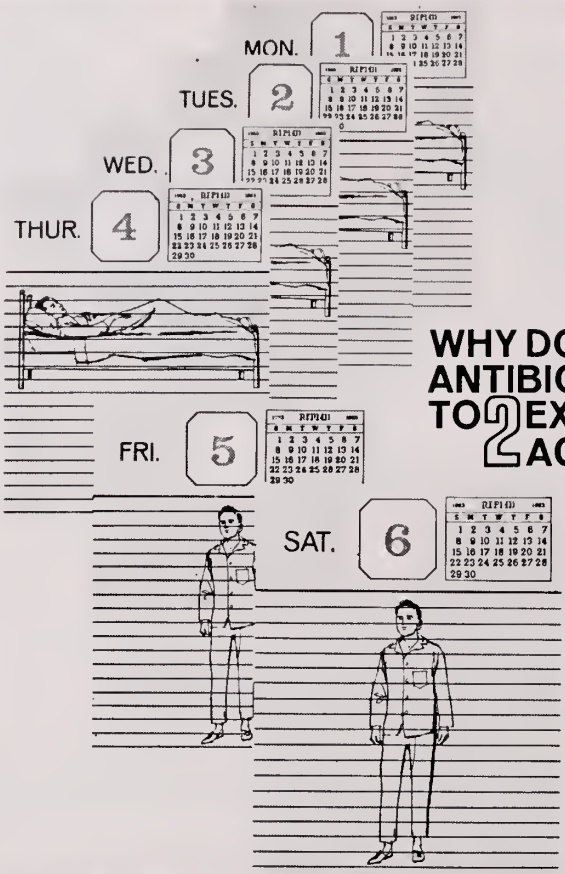
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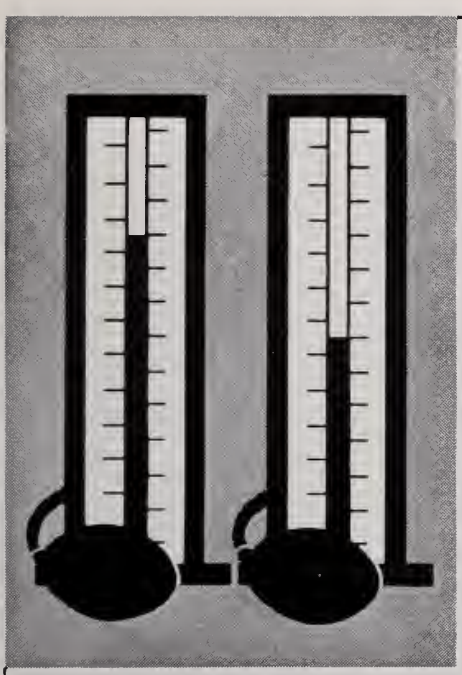
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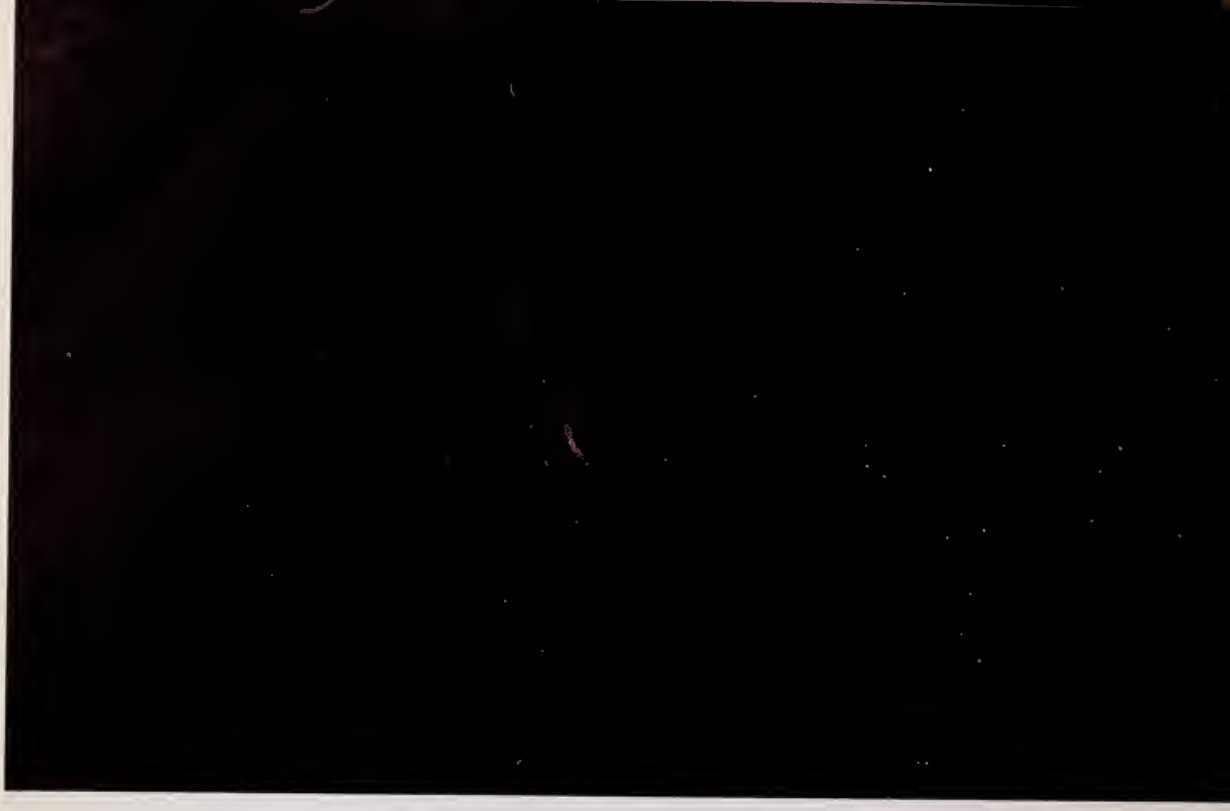
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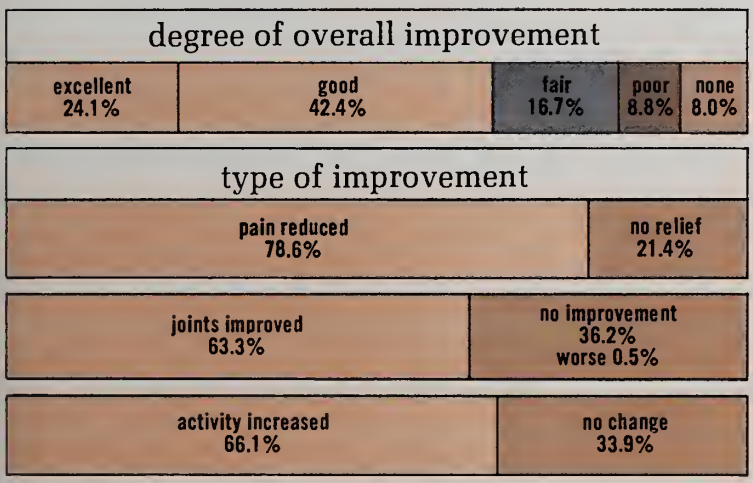

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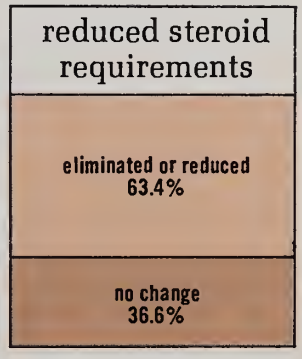
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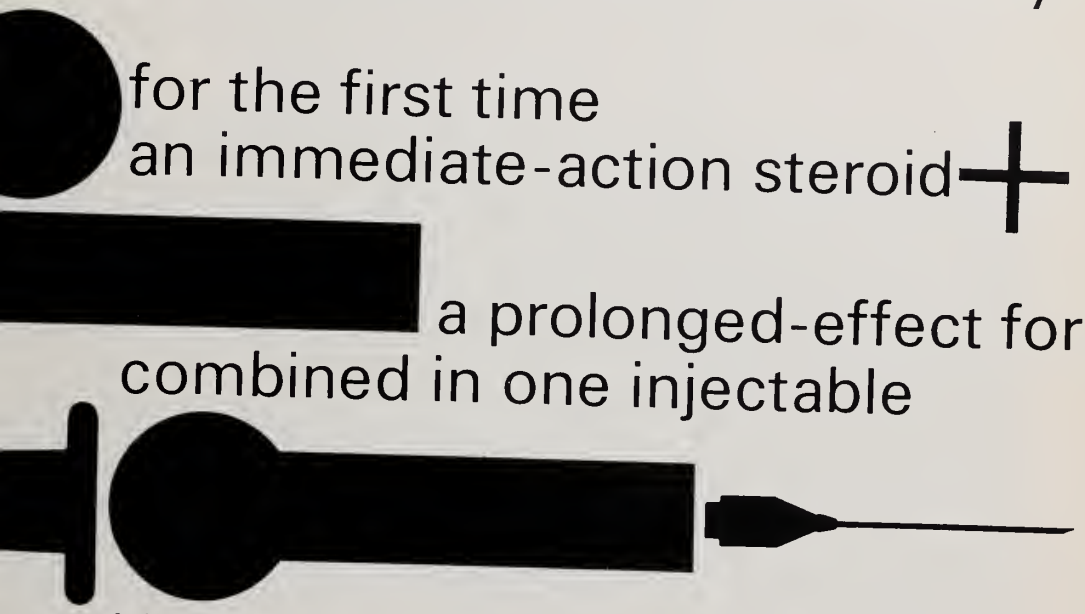
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CIRCUMOVAL PRECIPITIN TEST IN SCHISTOSOMIASIS MANSONI
A Study of 400 Patients

R. Rodríguez-Molina, M.D., Sc. O (Med.), FACP
J. Oliver-González, Ph. D.
A. Rivera-de Sala, M.T., M.S.

Schistosomiasis mansoni occurs in about 15% of the population of Puerto Rico. The diagnosis is established by demonstration of ova in the stools or rectal biopsy.

The great majority of infections seem to be acquired during childhood or adolescence. Experience has demonstrated that in infections of many years duration, ova may be difficult to find by direct examination of feces, or in the rectal biopsy, so that results may be equivocal. On the other hand, blood serum from chronic cases still preserves the antibody activity related to the circumoval test many years after infection.

In 1954 (1) Oliver-González devised a serological test which has been evaluated at the Veterans Administration Hospital in San Juan. In this test ova from laboratory strains of the parasite are suspended in the serum from a suspected case, human or animal. A positive reaction is the formation of a precipitate around the egg membrane, an indication of the presence of antibodies in the patient's serum. Hence the designation "circumoval precipitin test". In the initial experiment sera from 49 individuals known to have chronic infection were found to be positive. It was also observed that the precipitin reaction became weaker or negative after treatment with the anti-schistosomal drug stibophen)Fuadin ®).

In 1956 (2) we reported a positive circumoval reaction in 43 out of 46 cases (93%), and in 1962 (3), of 300 cases studied, 96% were positive.

The circumoval reaction is species-specific and thus may be used to differentiate between the three human species, *S. mansoni, S. japonicum,* and *S. hematobium* (4). In Puerto Rico, however, we are chiefly interested in *S. mansoni,* the only one found.

The present report deals with an evaluation of the circumoval reaction in 400 cases of Manson's schistosomiasis.

From the General Medical Research Laboratory and Medical Service, Veterans Administration Hospital, and the Department of Medical Zoology, University of Puerto Rico School of Medicine, San Juan, Puerto Rico.

Material and Methods

Three hundred subjects were male Puerto Rican veterans whose ages ranged from 30 to 68 years. About 30% of them were also infected with intestinal parasites, such as *Ascaris,* hookworm, and *Trichuris.*

One hundred other subjects included a group of men, women and children (ages 4 to 62) who lived in an endemic area and who were treated with stibophen (Fuadin ®). Amount of drug administered to each individual ranged from 20 to 180 ml. A second circumoval test was done on each individual 3 to 44 month after treatment; 3 to 5 stool specimens were examined.

In all those cases the circumoval test was done as soon as diagnosis was made by demonstration of ova in the feces or rectal biopsies.

Circumoval tests were performed in sera from 100 additional individuals apparently not suffering from schistosomiasis, used as uninfected controls.

Preparation of Circumoval Test

Material and Apparatus: To obtain sera, about 5 ml of venous blood were withdrawn from cubital veins and allowed to coagulate. Other materials and apparatus were: livers from 2 to 4 mice or hamsters, which had been infected with *S. mansoni* 8 to 10 weeks previously, electric blender (washed

with distilled water), 2% saline, at room temperature, sera from infected animals or human subjects that have been inactivated for 30 min at 56°C, a set of sieves (mesh 40, 60, 80, and 100) to fit the test cup (250 or 500 ml), filtering flask, 1,000 ml, rubber tube with aerating stone, separatory funnel, suction and extraction pump, culture tubes, glass slides and cover slips, petroleum jelly, and capillary pipettes with rubber bulbs.

Procedure: (5) After crushing a piece of liver between 2 slides and examining it for ova, livers were homogenized for 3 min in the blender, using 1.7% saline, 1 to 2 inches of saline in bottom of the blender cup. (The 1.7% saline is used to prevent hatching of the eggs). The homogenized mixture was transferred to a beaker and passed through sieves and rinse blender cup with more saline into a test cup. Two percent saline was allowed to flow drop by drop through rubber tube and aerating stone to bottom of filtering flask. Saline comes out of outlet on side of cylinder, thus washing the eggs. The clear homogenized mixture was allowed to sediment for 15 min. By means of suction the supernatant fluid was removed and the ova remaining in the bottom were transferred to a separatory funnel. The egg suspension was allowed to remain in the separatory funnel for 5 minutes, then the saline was allowed to come out drop by drop through the funnel. The eggs will stick to the walls of the funnel, becoming cleaner. Saline was added to the funnel and the clean eggs suspension was transferred to a test tube.

Concentration of egg suspension to be employed as antigen was determined. The number of eggs per drop to make a suspension in saline of 100 eggs per drop were counted. One drop of serum and one drop of egg suspension were placed on a slide and covered with a petroleum jelly bordered cover slip. The preparation was incubated overnight at 37°C and read under the microscope next morning. Reaction around eggs (hyaline, finger-like projections, sometimes septate) taking care to distinguish true precipitates from artefacts or bacterial contamination. All ova and those with precipitate around them were counted, noting length of precipitation.

Results were recorded under following headings: Name of patient or animal, date of test, positive control serum, number of ova on slide, number of positive ova, length and form of precipitates to determine the intensity of reaction (whether weak, moderate, or strong). Reactions were then graded 1 to 4+ according to the length of precipitate.

Results

A positive circumoval reaction was obtained in 368 individuals or 92%. The tests performed in 100 non-infected individuals were all negative.

With reference to the value of the circumoval test as an indication of improvement or curability following treatment, results obtained are considered poor. (Table II). Only about 11% of treated cases gave a negative circumoval test, yet examination of stools in this group revealed a much higher percentage (45.7%) of negative stools. That is, there was lack of agreement between a negative circumoval test and negative stools in this group of patients.

Discussion

The incidence of positive circumoval reaction in 92% of a large number of patients with active schistosomiasis, and no false positive in non-infected patients, indicates a high level of diagnostic reliability.

These results compare favorably with those observed by others in Puerto Rico. Anderson and Naimark (6) in 1960, obtained 88% positive reactions employing the same method among 506 proven cases of schistosomiasis mansoni.

In 1962 Pellegrino and Oliveira Andrade (7) working in Brazil performed circumoval

tests in 164 patients with active schistosomiasis. The test was positive in 71% of cases, which is not as high a figure as obtained by the above mentioned investigators and by us.

The circumoval reaction appears to be a true antigen-antibody reaction, an immunochemical interactions between the antigenic substance present in the ovum and the specific antibody stimulated by it in the infected host. The precise nature and location of the antigenic substance in the eggs has not been clarified. Electrophoresis studies by Cancio (8) have located the antibody in the gamma fraction of the patients' sera. The gel filtration technique was employed by Toro-Goyco (9) to fractionate samples of sera from individuals infected with *S. mansoni*. The specific antibody which was present in the serum of these individuals and which has been found to react with the *S. mansoni* ova, yielding a positive circumoval precipitin test, was found to be a normal size gamma globulin with a sedimentation coefficient of 6.6 Svedberg units, and a molecular weight close to 200,000. Partial enzymatic hydrolysis of this protein was found to alter the immunological properties, rendering the circumoval test negative after incubation with reactive ova, indicating that the chemical integrity of the protein is needed to yield a positive circumoval reaction.

Since false positives may occur in serologic tests, we are currently studying this factor. It is conceivable that diseases in which abnormal blood proteins and high gamma globulins are likely to occur, such as sarcoidosis, multiple myeloma, collagen disease, nephrotic states and cirrhosis of the liver, might cause false positive circumoval reactions.

We are working with sera obtained from patients suffering from these conditions, who have not lived nor visited in areas where schistosomiasis is prevalent. So far, in sixty patients studied, the circumoval precipitin reaction has been negative.

No serologic reaction based on the formation of an antigen-antibody complex is 100 per cent accurate. False positive as well as false negative reactions are bound to occur.

If a patient showing ova in his feces gives a negative circumoval reaction, as occurred in a small percentage of cases, we may assume either that the ova are non-viable and the disease is already arrested, or that the individual has not reacted immunologically to the specific protein antigen.

Now, what does a positive circumoval test indicate?

Studies performed at this laboratory (10) in mice infected with *S. mansoni* and treated with stibophen (Fuadin ®) for a prolonged period of time (over 200 days), have shown that when the circumoval reaction was positive during life, viable eggs and living worms were found at autopsy; and that a negative circumoval test when observed during life was related to extermination of infection, as indicated, at autopsy, by changes in tissue reaction from an active inflammatory type of tissue reaction to a quiescent, cicatricial type. (Figures 2 and 3).

If one accepts these changes in an animal that reproduces the disease as it occurs in man, then, we can say that a positive test in man indicates active infection with living worms associated with the presence of viable eggs in the tissues.

As stated above, only about 11% of treated cases gave a negative circumoval test, yet examination of stools in this group reveal-

ed a much higher percentage (45.7% of negative stools. That is, there was lack of agreement between a negative circumoval test and negative stools in this group of patients. This may be explained by the known transitory supressive effect of stibophen on oviposition.

The most important drawback of the circumoval test is that it requires the eggs obtained from mice infected with cercariae at the laboratory. This is a time consuming procedure requiring a period of eight weeks. Cercariae are obtained from snails collected in bodies of fresh water such as rivers or ponds. Experimental raising of snails and their infection in the laboratory is even more time consuming and difficult. For these reasons the test cannot be employed as a public health measure for mass diagnosis, that is, to cover large numbers of individuals in a short period of time, in the manner of a tuberculin or histoplasmin test.

One of us (A. R. S.), (11) has demonstrated that schistosome ova preserved by a process of lyophilization (Figure 1) have given a positive circumoval reaction sixteen months after extraction of ova from freshly killed mice. If eggs can be thus preserved and then produce a reaction similar to that obtained in the fresh state, the circumoval precipitin test has progressed from a research to a practical procedure, one that can be easily performed at a hospital clinical laboratory or even at the doctor's office. A commercial laboratory could prepare lyophilized ova in glass vials to be used when setting up the test.

A rapid enzymatic method of separating schistosome ova from livers and intestines of mice in quantities sufficient for the circumoval precipitin test, recently has been developed at this hospital. High yield of ova have been obtained by digestion of the homogenized tissue with the proteolytic enzyme pinguinain. This substance is a very active enzyme, obtained from the fruit of a common plant that grows in Puerto Rico, which is related to the pineapple (12), *Bromelia pinguin L,* (Common name: maya).

A serum protein paper electrophoresis study of the sera of a group of 58 patients with chronic schistosomiasis was performed at this laboratory (13). All of them were tested with the circumoval precipitin reaction. It was found that the gamma globulin was signicantly higher in those sera that produce a large amount of precipitate (2+ to 4+) in the circummoval precipitin test that in those that produced either none or a small amount of precipitate (0 to 1+).

One of the factors affecting the formation of precipitates in any precipitin reaction is the relative concentration of antigen and antibody. At the zone of equivalence, where maximum precipitation occurs, these concentrations are equal or nearly equal. Concentration of the globulins obtained from strongly reacting sera (4+) resulted in precipitates which were comparable in size to those produced by the unconcentrated globulins from the same sera. Both the 4+ globulins and the 4+ concentrated globulins produced maximum precipitation. It appears that the antigen and antibody concentrations are nearly optimal in the 4+ reacting sera. *In vitro* studies have been performed to test whether the sera producing 1+ circumoval reactions contain the antiegg antibodies in lower concentrations

than the sera producing larger amounts of precipitate (2+ to 4+). It was found that the difference in magnitude of precipitates formed by 4+ reacting sera and 1+ reacting sera was highly significant. Results of these studies indicate that a 1+ reaction is a true positive reaction. The authors (14) postulate that the amount of precipitate formed in the circumoval reaction is a quantitative measure of the anti-egg precipitin antibodies present in the serum of animals or humans infected with the parasite *S. mansoni.*

Work now in progress at this laboratory related to quantitation of the circumoval test *in vivo,* (white mice), treated with stibophen, indicates that the circumoval precipitin reaction diminishes in intensity under treatment. It was possible to perform several tests in each animal during period of therapy in order to observe the effect of the drug on the magnitude of the reaction, that is, if a 4+ reaction would revert to a 1+ or even become negative, as treatment (repeated intramuscular injections of the the drug) increased.

Summary

The purpose of the study was to determine the reliability of the circumoval precipitin reaction, a serologic test for the diagnosis of *Schistosoma mansoni* infections, and to find out whether it can be used to appraise the effect of chemotherapy in this disease. The circumoval precipitin reaction was performed in blood sera from 400 individuals infected with the parasitic blood fluke *S. mansoni.* A positive test was obtained in 368 individuals or 92%. The test was also performed in sera from 100 persons of this group before and after administration of variable amounts of stibophen (Fuadin). Only about 11% of treated cases gave a negative circumoval test, yet stool examination revealed a 45.7% negative stools. One hundred other patients apparently not suffering from schistosomiasis were studied. Results indicate that the circumoval reaction is a reliable diagnostic tool, but at present it cannot be considered as another criterion to appraise effect of chemotherapy in this disease in man.

Advantages and drawbacks of the test are discussed. Other investigations on problems related to serology of schistosomiasis are also discussed.

Resumen

El propósito de este estudio consistió en determinar la validez de la reacción circumoval de precipitina, prueba serológica usada para el diagnóstico de infecciones por *Schistosoma mansoni,* e investigar su uso en la evaluacicn del efecto de la quimioterapia en esta enfermedad. La prueba circumoval de precipitina se llevó a cabo en los sueros sanguíneos de 400 individuos infectados con el parásito *S. mansoni.* De este grupo de individuos se obtuvo una prueba positiva en 368 o sea 92%. Se determinó la reacción circumoval en los sueros de 100 personas de este grupo antes y después de habérseles administrado distintas cantidades de stibophen (Faudin ®). Solamente alrededor de un 11% de los casos tratados dio una prueba circumoval negativa, aún cuando un 45.7% de este grupo tuvo exámenes de excreta negativos. Otro grupo de 100 pacientes que aparentemente no sufrían de esquistosomiasis fue estudiado con

resultados negativos. Los resultados obtenidos indican que la reacción circumoval es una prueba confiable como diagnóstico, pero en el presente no puede ser considerada como otro criterio más para evaluar el efecto de la quimioterapia en esta enfermedad en el hombre.

Las ventajas y desventajas de la prueba y otras investigaciones sobre problemas relacionados a la serología de la esquistosomiasis han sido discutidas.

Acknowledgement

We wish to express our appreciation to Dr. Joseph L. Rabinowitz, Veterans Administration Hospital, Philadelphia, Pa., and Drs. Armand Littman and Tito B. Dinzey of Veterans Administration Edward Hines Hospital, Illinois, who supplied sera obtained from patients suffering from conditions in which abnormal blood proteins are likely to ocurr. We are grateful to Dr. Lawrence Ritchie and Mrs. Wilda B. Knight from the U. S. Army Tropical Research Medical Laboratory.

TABLE I: CIRCUMOVAL TEST IN SCHISTOMASIS

Group	*Number*	*Positive*	% *Positive*
Schistosomiasis	400	368	92
Controls	100	0	0

TABLE II: CIRCUMOVAL TEST IN SCHISTOSOMIASIS RESULTS IN TREATED CASES

			Negative Stools		Negative Circumoval
Individual	Amount of Drug	Cases	%	Cases	%
91	20 - 60 ml	32	38.5	10	10.9
9	61 - 180 ml	6	7.2	0	0



Figure 1: Circumoval precipitate observed after incubation of lyophilized *S. mansoni* eggs in immune human serum. Eggs were preserved by lyophilization for nine months before preparation of test (X 340).

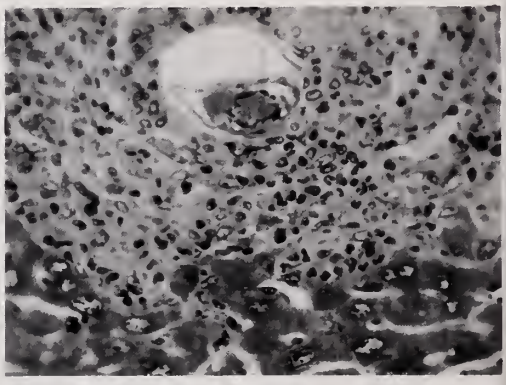


Figure 2: Mouse No. 109 (210 days after initial exposure), Circumoval test: 4+. Hematoxylin-Eosin, 430 magnifications. Shows infection still active, egg with mature degenerating miracidium, surrounded by large pseudotubercle containing histoid cells, lymphoid cells and numerous polys. Pigment particles are scarce, adjacent liver cells are largely normal, but reticuloendothilial cells are prominent.

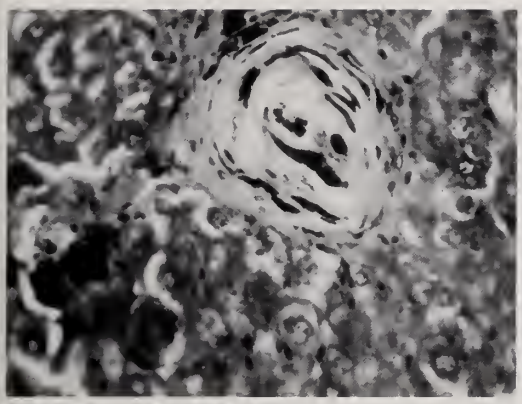


Figure 3: Mouse No. 206B (280 days after beginning of treatment or 350 days after initial exposure). Circumoval Test, negative. Eggs shell without embryo, in the center of a concentric scar, representing a treated pseudotubercle in liver. Calcium and pigment granules also present, the latter abundant and intracellular. No active inflammation remains.

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ELECTROPHORESIS OF SERUM PROTEINS IN CLINICAL PRACTICE

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María E. Belaval, M. T., M. S.
Amina Rivera de Sala, M. T., M. S.
Marta Cancio, Ph. D.

Ten years of filter paper electrophoresis in the Veterans Administration Hospital, San Juan, Puerto Rico, have left us in the possesion of nearly 1500 trcings (pherograms) and a doubt... a doubt that eventually came to be expressed in the question — how useful has this method proven to be in the diagnosis and management of disease? This paper is the result of the analysis of our material in the search for an answer to this question.

Materials and Methods

Our initial attempts at electrophoresis were conducted with a crude home-made apparatus which, despite its limitations, allowed us to recognize the first cases of mixed hemoglobinopathies in Puerto Rico. We soon acquired a commercial apparatus and this whole study deals with material analyzed with the Spinco (Beckman) equipment by the same technician using the same standard techniques.*

When we started filter paper electrophoresis of the serum proteins we were mainly looking for diagnostic patterns in protein disturbances in disease as reflected in the distribution chart. We were chiefly interested in the information conveyed by visual examination of the tracing itself, without reference to chemical determinations of serum proteins. The pherogram was to be utilized in the manner that the electrocardiogram usually is: a diagnostic tool based primarily on the characteristics of a tracing. One result of the analysis of our data has been to bring to our attention the considerable value of another piece of information that can be obtained directly from the pherogram, the percentage distribution of the protein fractions.

We have encountered some serious difficulties in the analysis and interpretation of the data. One is the frequency of multiple diagnoses in the same patient —to which diagnosis is one to attribute the electrophoretic pattern? This problem has resulted in the elimination of a good deal of the material; we have based our conclusions on data that proceeds from patients in whom we are reasonably sure of the diagnosis responsible for the changes. Even so one is forced to classify under one diagnosis patients with different clinical levels of a disease so that the pattern that emerges may not be truly characteristic of the active disease.

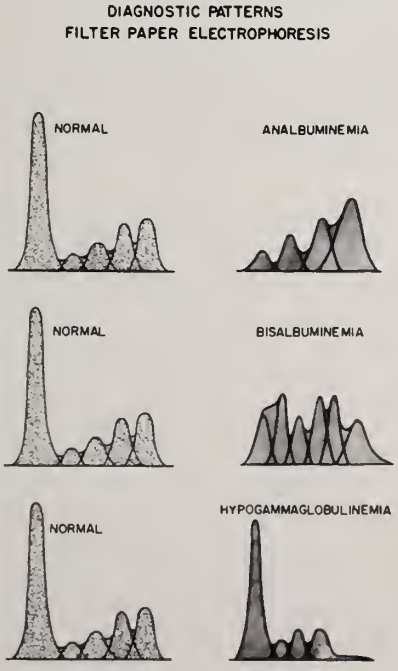
From the General Medical Research Laboratory and the Medical Service, Veterans Administration Hospital, San Juan, Puerto Rico.

* *A method for serum proteins using Bromphenol Blue in aqueous solution. (Spinco Procedure A). Technical Bulletin 6095A, published by Spinco Div., Beckman Instruments, Inc., Stanford Industrial Park, Palo Alto, Calif.*

Another problem has been the choice of suitable normal control values. In order to be able to recognize the abnormal, one must first be familiar with the normal. Our normal controls drawn from healthy VA employees gave values considerably different from the two other Puerto Rican groups (1-2) studied before (Table I). Our insular values in turn differed considerably from the values of 31 paper electrophoretic surveys conducted among the healthy all over the world and compiled by Wuhrman and Wunderly (3). Our solution was to extend the range of normals to include the extreme values of all the data at hand. Thus we branded as abnormal, values beyond these ranges: Albumin, 48-73%; α_1, 1-7%; α_2, 3-14%; β, 7-20%; γ, 12-23%.

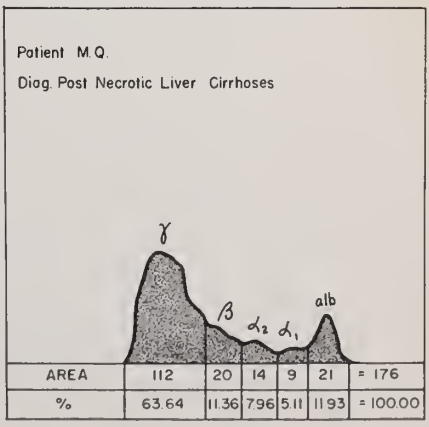
Results and Comments

We will start by reviewing our data on those disease where filter paper electrophoresis is considered a diagnostic tool (Figure 1).



Bisalbuminemia, analbuminemia, and agammaglobulinemia are foremost in this list. Here the pherogram establishes the diagnosis by itself. Bisabulminemia is usually a congenital disorder, but may be acquired and transitory. Recent work with starch block electrophoresis (4) suggests that normal human albumin composition is ruled by two codominant alleles — the very rare heterozygote is bisalbuminemia. Analbuminemia is a familial disorder described from Germany associated with mild edema. Hypogammaglobulinemia is a much more frequent abnormality than the other two — there is a hereditary form first described by Bruton (5) and associated with susceptibility to infection, but more common is the acquired form associated with certain disease processes such as multiple myeloma.

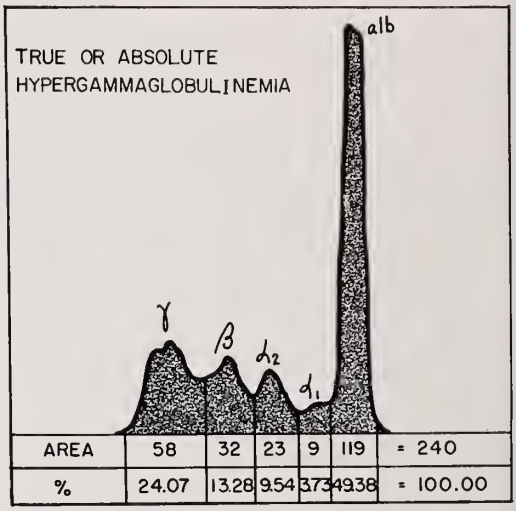
Upon review of our material we failed to find a single case of either *analbuminemia* or *bisalbuminemia*. We found some tracings with very little albumin indeed, but this was always due to a known disease process. We have listed in this table (Table II) our cases of *hypoalbuminemia*.



If you consider that 48% is the lowest range of normal you will readily appreciate that these patients had severe hypoalbuminemia. While cirrhosis of the liver is the disease most commonly associated with these low values, the hypoalbuminemia of nephrosis carries a worse prognosis and that of Hodgkins, the worst of all. Fifty per cent of the patients with hypoalbuminemia below 32% were dead within 1 year. On the other hand the lowest values of all, 5.10%, corresponds to a patient with the nephrotic syndrome who is still alive and now well.

While hypoalbuminemia is a relatively common abnormality, its opposite, hyperalbuminemia, does not seem to occur at all. Yet we came across a patient in our series who had an albumin of 74.4%, which goes beyond the universal extreme high normal range of 73%. This patient also had an extremely low beta and his diagnosis was hypochromic anemia due to uncinariasis.

As far as *hypogammaglobulinemia* is concerned, again we did not identify a single case of the congenital disorder, but we came across 25 cases of the acquired type in relation to other diseases including multiple myeloma (Table III). We were surprised to find that four cases ot hypogammaglobulinemia were accounted for by Buerger's disease, and looking further into this matter, found that out of 18 cases that bear this diagnosis, 7 have gamma globulins below 14.7 which is considerably below the mean normal value in the three Puerto Rican groups. Predictably, the greatest incidence of hypogammaglobulinemia occurred in the nephrotic syndrome.



AREA	58	32	23	9	119	= 240
%	24.07	13.28	9.54	3.73	49.38	= 100.00

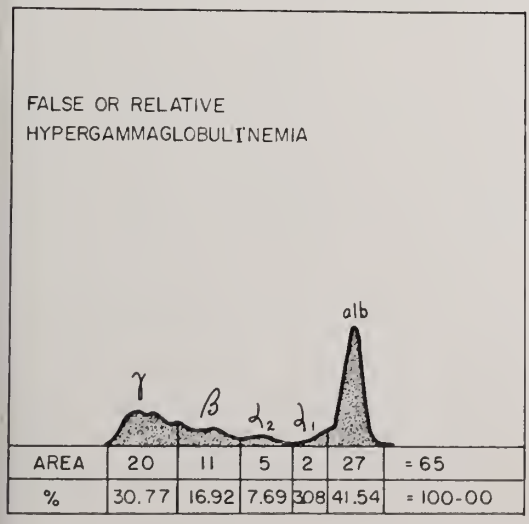
Apart from analbuminemia and hypogammaglobulinemia, we know of no other congenital deficiency of a protein fraction but many diseases are known to produce abnormal fluctuations of these fractions and for the sake of clarity these fluctuation will be considered now. Rather than patterns we study for this purpose the percentage distribution of protein fractions as compared to normal.

Hypergammaglobulinemia — the antithesis of hypogammaglobulinemia is a well recognized and frequent serum protein abnormality (Table IV). Our data agrees with that of others; the collagen diseases appear to be a major cause of this abnormality, as well as cirrhosis of the liver, particularly the post-necrotic type as this case responsible for the highest gamma globulins values in our series illustrates (Figure 2). Hypergammaglobulinemia can be absolute or relative and one does not need appeal to chemical determinations to settle this point. Figure 3 (A, B) illustrates both si-

tuations. If filter paper electrophoresis is carried out invariably by the same technician and the same methods, apparatus and material, one can draw rough quantitative measurements of protein from it. Thus, one can judge whether one is dealing with a relative or absolute increase or decrease of a protein.

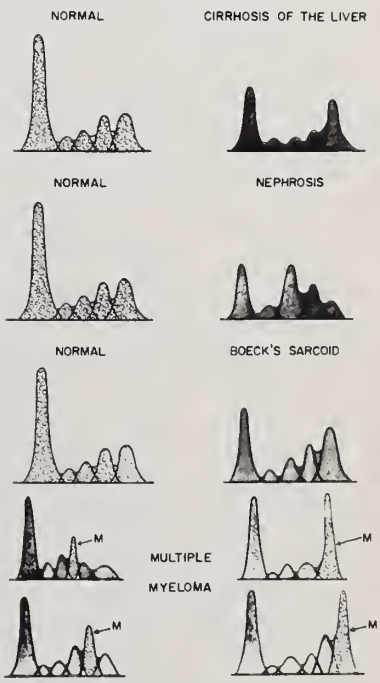
In the case of α 1 globulin the study has yielded very interesting results. Table V details the diseases related to *hyper-*α1 *globulinemia,* and the grave prognosis that is attached to it. We were able to investigate the fate of 40 of these 60 patients and only six of them were alive one year later. According to the material in our study, whenever a case shows this abnormality the chances are 2:1 that one is dealing with a malignant disease — cancer, lymphoma or leukemia.

Hyper.- α2 *globulinemia* was found to be one of the most common protein deviations from normal in disease. Here again the collagen diseases are the chief architects closely followed by heart disease and cancer (Table VI).



AREA	20	11	5	2	27	= 65
%	30.77	16.92	7.69	3.08	41.54	= 100.00

CHARACTERISTIC PATTERNS
FILTER PAPER ELECTROPHORESIS



Hyper and *hypo-* β *-globulinemia* are relatively rare in our series. Nephroses accounted for most of the cases of hyper- β -globulinemia and cirrhosis of the liver was the only condition to produce two cases of hypo- β -globulinemia and that because of fusion with the gamma globulins (Table VII and VIII).

Finally, we have the diseases in which the serum protein pattern itself is characteristic enough to be of diagnostic value. These are multiple myeloma, cirrhosis of the liver, nephrosis and sarcoidosis (Figure 4). Here again our material agrees with the published literature on these subjects — the pherogram allows a clear recognition of nephrosis — the low albumin and gamma globulin and the tall α_2 are characteristic. As mentioned before, the pattern of hypergammaglobulinemia and hypoalbuminemia in cirrhosis of the liver occurs in our material. Sarcoidosis is one disease where observation of the pattern is more useful than knowledge of the percentage of the proteins. Sunderman (6, 7) has popularized the concept of the sarcoid steps — the characteristic step-like pattern of the pherogram. Of 26 cases with a clinical diagnosis of sarcoidosis in our series, only a minority, 7 (about 27%) showed the characteristic pattern. Of these 7 cases, five were considered clinically to be subacute cases and two chronic. One case clinically subacute gave a normal electrophoretic pattern.

Our patients with multiple myeloma with satisfactory protein studies totalled 17 (Fig. 5). We notice that patients with

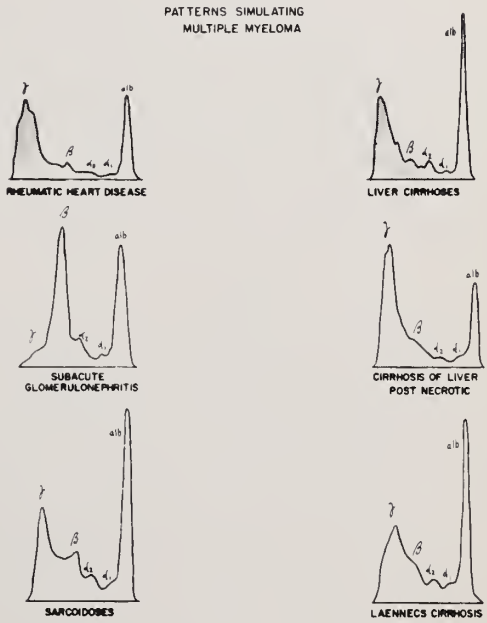
	NAME	AGE	ELECTROPHORETOGRAM	TYPE	SERUM PROTEINS Gm.%	URINE FOR BENCE JONES	URINE PROTEIN MOBILITY	LIFE DURATION IN MONTHS	CLINICAL PATTERN
1	A.D.	62		$\gamma_{(A_2)}$	A3.8 G1.8	NEG.		42	INITIAL LESION PLASMA CYTOMA CERV. VERTEBRA TERMINAL SPREAD TO OTHER BONES. NO ANEMIA. EVER CEREBRAL HYPERTENSION. RETROBULBAR NEURITIS NO AUTOPSY.
2	G.U.	60		β	A2.0 G6.3	NEG.		18	PRESENTING PICTURE PERICAROTITIS. BONY LESIONS. DIED WITH PURPURA, HEART FAILURE, LIVER FAILURE, INFECTION NO RENAL DISEASE AUTOPSY
3	V.N.T.	29		γ	A4.3 G3.5	NEG.		42	INITIAL LESION PLASMA CYTOMA OF LEFT HIP SPREAD TO STERNUM LATER ON NO RENAL DISEASE NO AUTOPSY
4	J.D.	65		γ	A3.2 G4.6	POS.		7	NEGATIVE BONE SURVEY AND NO BONE LESIONS AT AUTOPSY. DIED OF STAPH BRONCHOPNEUMONIA URETHANE. BONE MARROW APLASIA AUTOPSY
5	M.M.	42		γ	A3.1 G11.1	NEG.		3	EXTENSIVE BONE LESIONS COAG. POS. STAPH AUREUS ENTEROCOLITIS NO RENAL DISEASE AUTOPSY
6	P.M.	66		γ	A3.8 G5.7	NEG.		10	BONE LESIONS. SEVERE HYPERTENSION BEFORE MULTIPLE MYELOMA RENAL FAILURE NO AUTOPSY.
7	E.F.	63		γ	A2.25 G6.40	NEG.		11	BONE LESIONS AMYLOIDOSES. DIED IN KIDNEY FAILURE NO AUTOPSY.
8	A.R.	67		$\gamma_{(A_2)}$	A1.8 G4.5	NEG.		0	BONE SURVEY NEGATIVE. RENAL DISEASE. HE WAS A DIABETIC WITH GLOMERULOSCLEROSIS AUTOPSY.
9	J.O.	71		γ	A1.75 G11.45	NEG.		10	BONE LESIONS NO AUTOPSY
10	E.R.	72		γ	A2.4 G4.2	NEG.		13	BONE SURVEY NEGATIVE FURUNCULOSES NO RENAL DISEASE APPARENT NO AUTOPSY
11	L.R.R.	38		γ	A2.7 G5.5	NEG.		39	STARTED AS PLASMACYTOMA BETWEEN 0.4-6 NO EVIDENCE OF RENAL DISEASE NO AUTOPSY
12	A.V.	65		γ	A1.8 G6.0	NEG.		4	BONE SURVEY NEGATIVE BUT SKELETON INVOLVED AT AUTOPSY MYELOMA KIDNEYS-RENAL FAILURE AUTOPSY
13	A.M.	68		α_2	A3.8 G3.0	NEG.	γ	3	BONE SURVEY NEGATIVE EXCEPT FOR OSTEOPOROSES NO RENAL FAILURE NO AUTOPSY
14	P.M.	75		$\gamma_{(A_2)}$	A1.4 G9.16	POS.	γ	1	BONE LESIONS NO EVIDENCE OF RENAL DISEASE DIED OF BRONCHOPNEUMONIA AUTOPSY
15	C.R.	70		$\gamma_{(A_2)}$	A1.59 G10.41	NEG.		8	BONE LESIONS. NO RENAL DISEASE. BILATERAL BRONCHOPNEUMONIA AUTOPSY
16	M.R.	67		β	A3.4 G3.35	NEG.	β	15	EXTENSIVE SKELETAL INVOLVEMENT. THROMBI IN PULMONARY ARTERY AND ASCENDING AORTA AUTOPSY.
17	N.M.	48		β	A1.4 G10.6	NEG.		11	BONE LESIONS NO RENAL DISEASE APPARENT STILL ALIVE

the solitary plasmacytoma type of the disease often do not show the characteristic church-spire abnormal globulin that characterizes the disease. Needless to say, a patient may have then a plasmacytoma without protein changes whatsoever - this point is now established beyond doubt as far as the filter paper pherogram is concerned. Our series do not allow us to conclude that there is any relation between the clinical course of the disease and the location of the abnormal protein. This abnormal protein may be located anywhere between the gamma and the $\alpha 2$ globulin. However, no matter their electrophoretic migration, these proteins are all immunoglobulins as can be proven by immunoelectrophoresis.

Our multiple myeloma cases are similar to others in the literature in the sense that most were of the gamma globulin type —13 out of 17. Unusual is the low frequency with which Bence-Jones protein was found in the urine; 2 of 17; the lowest that we know of.

In Figure 6, we depict a few of our cases not having multiple myeloma but with pherograms simulating the characteristic ones for that disease. Other notorious multiple myeloma impersonators are Waldestrom's macroglobulinemia and Franklin's disease.

Thus multiple myeloma may not show protein abnormalities at all by electrophoresis and other diseases may show the protein abnormalities of multiple myeloma. however, one must remember that these are exceptions.



Space does not allow us to go into other less important abnormalities and diagnostic patterns in serum protein electrophoresis. Such are fusion of different fractions such as gamma and beta in some cases of liver cirrhosis and splitting of the β or $\alpha 2$ as occurs in other diseases besides multiple myelomas. We found a few of these cases.

Conclusion

In conclusion, how should we answer the question that we formulated at the begining? How useful is filter paper electrophoresis to a hospital like ours? We must pronounce it a useful but not an indispensable diagnostic tool. The evidence is that it is only diagnostic in diseases that

are so rare as to be of no practical importance. There is no important disease where the diagnosis cannot be established by other means. Yet we have detailed some practical diagnostic and prognostic implications that can be derived from it. Moroever, it is an important research tool.

Resumen

Después de practicar la electroforesis de proteínas del suero en papel por diez años en nuestro hospital, nos hemos preguntado, ¿cuán útil ha sido este procedimiento en el diagnóstico de las enfermedades y manejo de los enfermos? Este trabajo es en sí un resumen de nuestro análisis de los datos buscando una contestación a la pregunta. No encontramos en nuestro material caso alguno de analbuminemia y agamaglobulinemia congénitos. La hipogamaglobulinemia e hipoalbuminemia secundarias a otras enfermedades fueron sin embargo frecuentes. La hipoalbuminemia severa parece asociarse con un pronóstico grave. Asimismo encontramos que una hiperalfaglobulinemia era a menudo de gravísimo pronóstico. Entre las causas frecuentes de hipogamaglobulinemia nos sorprendió encontrar a la enfermedad de Buerger. Se repasa nuestra experiencia con el mieloma múltiple, sarcoidosis, cirrosis de hígado y nefrosis donde los cambios en las proteínas son a menudo patognomónicos y señalamos algunas excepciones.

En fin, después de considerar que no hay ninguna enfermedad importante donde el diagnóstico se establece exclusivamente por el electroforesis del suero concluímos que esta es una prueba útil pero no indispensable para la práctica de la medicina en un hospital moderno.

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TABLE I: NORMAL CONTROLS

	Alb.	α_1	α_2	β	γ
Present series	Mean	Mean	Mean	Mean	Mean
20 healthy V. A. employees	56.14	3.80	8.80	14.72	16.34
Ages 30 to 53 yrs.					
	Range	Range	Range	Range	
Puerto Rico	49.33 to 64.02	2.55 to 5.45	5.95 to 13.47	10.58 to 19.10	13.48 to 21.08
Mean values - 37 healthy adults					
Ages 23 to 66 years	48.7	4.4	10.2	13.9	22.7
Ramírez, Elí A., et al.					
Puerto Rico					
Mean values - 51 healthy adults					
Ages 20 to 59 years	50.7	4.3	9.8	14.4	20.8
Suárez, et al.					
Puerto Rico					
	Mean	Mean	Mean	Mean	Mean
Values of 31 series worldwide (Wuhrman and	60.9	4.2	8.2	11.5	15.2
Wunderly)	Range	Range	Range	Range	Range
	49.1 to 72.9	1.4 to 6.5	3.5 to 10.6	7.3 to 15.1	12.4 to 22.2

TABLE II: FORTY TWO CASES OF HYPOALBUMINEMIA

Diagnoses	*Number of cases*	*Number dead within 1 yr.*
Nephroses and Nephrotic syndrome	11	8
Cirrhosis of the liver	13	4
Hodgkins	5	5
Cancer	4	3
Chronic Granulocytic leukemia	2	2
Reiter's disease	1	0
Rheumatic heart disease	1	0
Multiple myeloma	1	0
Pulmonary TBC	1	0
Chronic pancreatitis	1	0
Whipple's disease	1	0
No diagnoses	1	0

Range in % Pherogram: 5.10 to 31.65%
Range in Gms: 0.9 to 3.1 gm %

TABLE III: HYPOGAMMAGLOBULINEMIA *

Diagnoses	*Number of Cases*
Nephritis-nephroses	6
Buerger's diseases	4
Sarcoid	3
Multiple myeloma	2
Miscellaneous	10
Total	25

* *Less than 12% Normal Range*: 12.4 to 22.7)

TABLE IV: FIFTY SIX CASES OF HYPERGAMMAGLOBULINEMIA *

(Excluding Multiple Myeloma)

Diagnoses	Number of Cases
Collagen Disease	15
Cirrhosis of Liver	9
Glomerulonephritis	7
Cancer	3
Chronic Pancreatitis	2
Bronchietases	2
Chronic Cholecystitis	2
Chronic Brain Syndrome	2
T B C	2
Thrombophlebitis	2
Others	10

* *Range: 24.07 to 63.54% (Normal: 12.4 to 22.7)*

TABLE V: HYPER $\alpha 1$ *

Diagnoses	Number of Cases
Lymphoma	10
Cancer	12
Renal disease	5
Hepatitis	4
Chronic pancreatitis	2
Heart disease	4
Leukemia	2
Cirrhosis of liver	3
Schistosomiasis	2
Infection	3

* *Larger than 7%*

TABLE VI: HYPER α 2 GLOBULINEMIA

(More than 14%)

Diagnoses	Number of Cases
Collagen disease	17
Heart disease	15
Cancer	15
Renal disease	11
Lymphoma	6
Chronic pancreatitis	3
Gout	3
Buerger's disease	3
Sarcoid	3
Diabetes mellitus	3

HYPO α 2 GLOBULINEMIA

(LESS THAN 3%)

Multiple myeloma	1

TABLE VII: HYPER β GLOBULINEMIA
>20%

Disease	No. Cases
Nephroses	3
Schistosomiasis M.	2
Chr. Panchreatitis	1

TABLE VIII: HYPO β GLOBULINEMIA
<7%

Disease	No. Cases
Cirrhosis of Liver	2
Hookworm Anemia	1
Sickle Cell Anemia	1
Chr. Pancreatitis	1
Renal Disease	1
Organic Heart Disease	1

CIRCUMOVAL ANTIBODIES: MEASUREMENT IN EXPERIMENTAL SCHISTOSOMIASIS

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Amina Rivera de Sala, M. T., M. S.
R. Rodríguez-Molina, M. D., Sc. D., FACP.

In a previous communication from this laboratory (1), it was postulated that the amount of precipitate formed in the circumoval reaction is a quantitative measure of the anti-egg precipitin antibodies present in the serum of animals or humans infected with the parasite *S. masoni*. The present study has been carried out utilizing mice infected with the parasite *S. mansoni* under experimentally controlled conditions to test the postulated hypothesis. Serial determinations utilizing the same group of mice throughout the experiment, without sacrificing the animals, were possible by means of the orbital bleeding technic (2).

Materials and Methods

A group of forty mice was exposed to 75 cercariae per mouse. These animals were tested for ova in the stools and for circumoval precipitin antibodies in the serum, daily, starting on the 35th. day after infection until ova or antibodies were first detected. Pooled sera and feces of ten mice were utilized. Mice were bled weekly for two months after appearance of antibodies, and monthly thereafter. Surviving animals continued to be bled monthly up to 514 days, when the last one was sacrificed for histopathological studies.

Measurement of the precipitates formed after incubation of eggs in serum was done at various stages of this experiment in order to correlate the length of the precipitates with the stage of infection. The methodology used for the performance of the circumoval precipitin test (COP), and for measurement of the precitates has been described previously (1).

Results

The results of this study are summarized in Table I. Statistical evaluation of the data obtained is summarized in Table II.

Circumoval antibodies were first detected forty-two days after exposure to cercariae. Ova were detectable in the feces of the same animals on the forty-fourth day. The size of the precipitates obtained in the circumoval reaction increased significantly from 10 + 3 μ in length on the forty-second day. to 283 + 120 μ on the eighty-first day. Afterwards, a gradual diminution in the size of the precipitates was observed. At one year the precipitates measured an average of 28 + 8 μ . At the end of this experiment,

From the General Medical Research Laboratory, Veterans Administration Hospital, San Juan, Puerto Rico.

TABLE I: LENGTH OF CIRCUMOVAL PRECIPITATES AT INTERVALS FOLLOWING INFECTION.

Duration of Infection (Days)	Eggs Positive	Length of CPO mean	s. d.
1 10 39	0	0	0
42	11	10	3
43	11	9	3
44	16	12	3
45	14	13	3
46	20	17	2
50	8	30	8
53	5	31	10
60	44	127	72*
67	38	41	8
74	33	96	34
81	47	283	120
87	41	64	38
95	38	43	10
126	30	89	30
156	20	45	3
191	51	58	24
219	45	56	26
253	42	34	13
281	45	26	7
315	38	40	7
347	38	49	9
379	31	28	8
421	36	26	6
449	35	27	8
472	38	28	10
498	32	26	8
514*	34	21	5

* *Sacrificed for tissue examination*

TABLE II: SIGNIFICANCE OF DIFFERENCES IN LENGTH OF PRECIPITATES FORMED AT VARIOUS INTERVALS AFTER EXPOSURE TO CERCARIAE

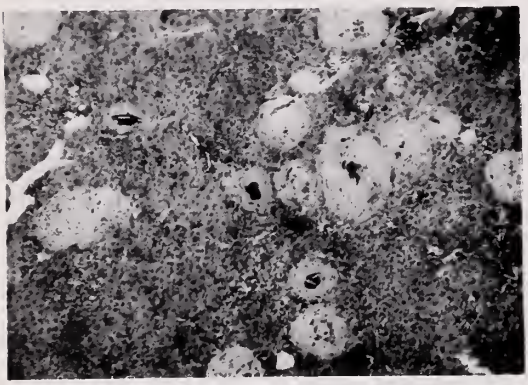
Days after infection	*Difference*	*Difference*[a]	*t*[b]	*Remarks* *Difference*	
42 and 50	+ 20	0.71	28.17	Highly Significant	$p < .001$
50 and 60	+ 97	6.31	15.37	Highly Significant	$p < .001$
60 and 74	− 31	6.54	4.74	Highly Significant	$p < .001$
74 and 87	− 32	4.02	7.96	Highly Significant	$p < .001$
87 and 95	− 21	3.23	6.50	Highly Significant	$p < .001$
95 and 126	+ 46	2.80	16.43	Highly Significant	$p < .001$
126 and 156	− 44	2.72	16.18	Highly Significant	$p < .001$
156 and 191	+ 13	7.77	1.67	Not Significant	$p > .1$
191 and 219	− 2	11.31	0.18	Not Significant	$p > .1$
219 and 253	− 22	9.21	2.39	Significant	$p < .05$
253 and 281	+ 8	4.65	1.72	Not Significant	$p > .1$
281 and 315	+ 14	3.15	4.44	Highly Significant	$p < .001$
315 and 347	+ 9	3.70	2.43	Significant	$p < .05$
347 and 379	− 21	3.86	5.44	Highly Significant	$p < .001$
379 and 421	− 2	3.22	0.62	Not Significant	$p > .1$
421 and 449	+ 1	3.18	0.31	Not Significant	$p > .1$
449 and 472	+ 1	3.95	0.25	Not Significant	$p > .1$
472 and 498	− 2	3.91	0.51	Not Significant	$p > .1$
498 and 514	− 5	2.86	1.75	Not Significant	$p > .1$

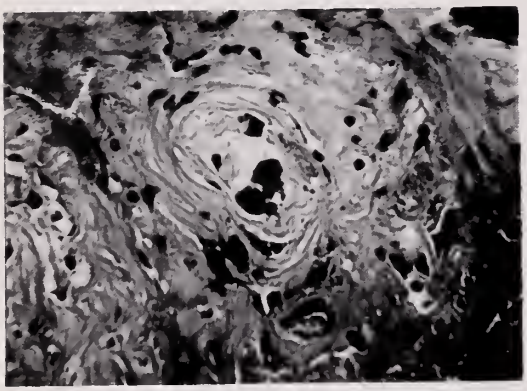
[a] σ Diff. $= \left[\frac{(X_1 - X_1)^2 + (X_2 - X_2)^2}{(n_1 - n_1) + (n_2 - 1)} \left(\frac{1}{n_1} + \frac{1}{n_2} \right) \right]^{1/2}$

[b] $t = (m_1 - m_2) / \sigma$ Diff.

when the only surviving animal was sacrificed for tissue examination (514 days after initial exposure), the precipitates obtained measured 21 + 5 μ in length (Table I).

At autopsy, gross examination revealed enlargement of the liver and spleen. One live adult worm was observed near the portal vein. Microscopic examination of both fresh and fixed liver and intestinal tissues showed empty shells, calcified eggs, pigmentation, and pseudotubercles surrounded by fibrous tissue (Figs. 1 and 2).





The data in Tables I and II is characterized by rapid increases in length of precipitates alternating with equally rapid decreases of apparently high statistical significance, up to 156 days after initial exposure to cercariae. Afterwards, the length of the precipitates decreased gradually, with fluctuations which were less pronounced and of little or no apparent statistical significance.

Discussion

The postulated hypothesis that the amount of precipitate formed in the COP reaction is a quantitative measure of the anti-egg precipitin antibodies present in the serum of animals or humans infected with the parasite *S. mansoni* seems to stand the test of measurement during experimental schistosomiasis produced after a single exposure of mice to cercariae.

Appearance of precipitates coincided with the stage of infection in which ova are first produced by the parasite. These precipitates are at first barely detectable measuring around 10 μ in length, but they increase in length very rapidly, having attained a length of over 100 μ by the end of the second month. Afterwards, the length of the precipitates decreases having reached lengths of around 30 μ by the end of one year after initial exposure.

Closer examination of the data discloses some fluctuations in the length of the precipitates at various stages of infection, for which a clear cut explanation does not exist at the present time. Since we are not certain of the reason for these fluctuations, two explanations, which could possibly explain the data, are offered conscious of the fact that they are mere speculations at the present time, and are open to future clarification.

The statistically significant fluctuations in the magnitude of the precipitates observed at various lengths of infection could be interpreted as corresponding to the immunological response of the host against antigenic substances present in the parasites eggs.

The first peak of antibody reaction may represent an initial response of the host to a first stimulus of egg antigen. The decrease in antibody concentration which follows may be the result of antibody inhibition or neutralization by egg antigen produced regularly by the worms. The response of the host's immunologic mechanism continues and is evident in the production of still more anti-egg antibodies, since a second and higher increase in the length of the precipitates is observed. Subsequent rises and falls of decreasing magnitude may be explained as a response to new challenges to the hosts immunologic mechanisms by the presence of new eggs being laid by the parasite worms. The gradual decrease in magnitude of the rises and falls observed may be explained as diminishing immunological response by the antibody synthetizing mechanisms of the host.

An alternate explanation is the possibility of production of primary and secondary antibody responses in the form of 19S and 7S molecules (3), respectively, producing the net effect already described. This hypothesis will be tested experimentally in the near future at this laboratory.

Summary

Quantitation of the circumoval precipitin test has been performed utilizing mice infected with the parasite *S. mansoni* under laboratory controlled conditions. Mice were bled at regular intervals by means of the orbital bleeding technic in order to utilize the same animals throughout the experiment. The first circumoval precipitates (10 in length), were detected 42 days after initial exposure. Length of precipitates increased rapidly, attaining maximal length of 283 μ at 81 days, after which length decreased rapidly at first, gradually later on. Observations were continued up to 514 days, when the only surviving mouse was sacrificed for tissue examination. Serum from this mouse produced precipitates of 20 μ in length.

Resumen

La prueba circumoval cuantitativa ha sido hecha en ratones blancos infectados bajo condiciones controladas en el laboratorio. Se sangraron los ratones a intervalos regulares por medio de la técnica del plexo orbital, haciendo posible utilizar los mismos ratones a lo largo del estudio.

Los primeros precipitados circumovales (10 μ de largo) aparecieron 42 días después de la infección. El largo de los precipitados aumentó rápidamente llegando a 283 μ a los 81 días. El largo disminuyó rápidamente al principio y gradualmente durante el resto del estudio hasta alcanzar un largo de 20 μ al finalizar el experimento. A los 514 días se sacrificó el último ratón que quedaba para examinar sus tejidos.

Acknowledgement

Dr. G. Ramírez de Arellano performed the histopathological studies. Dr. E. Toro-Goyco reviewed the statistical data and Dr. José Oliver-González reviewed the manuscript. Drs. Julio V. Rivera and R. Menéndez-Corrada offered helpful suggestions in the interpretation of the results.

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WHY, WHEN AND HOW OF COLOSTOMY FOR BOWEL TRAUMA

Lyndon E. Lee, Jr., M. D., F.A.C.S.

Minute simple, single or multiple punctures of the intestine or bowel demand no operation but may be treated by means of body and intestinal rest, with decompression and parenteral feedings supplemented by broad spectrum antibiotics. Fear of leakage from such lesions as needle punctures is unjustified.

However, discretion dictates exploration of all but the smallest penetrating wounds of the abdomen. This belief is based on proved saving of lives from wartime intestino-colic injury as well as on the strong probability of discovering in civilian practice correctible wounds of organs other than the bowel. Today multiple injuries to the gastrointestinal tract and other hollow or solid parts are common, often threatening intestinal and colonic blood supply as well as more major vessels. Occasionally the problem is complicated by bone injuries. The greatest danger in any penetrating wound of bowel is multiple perforations, with one or more going unrecognized and untreated. A particular hazard is perforation of the mesenteric border. All of these injuries must be looked for at the time of the original operation on the bowel. Their correction is a paramount consideration in immediate prognosis, and with early reconstructive surgery function of intestine, bowel and other organs may often be saved.

Present-day surgical practice is increasingly complicated by injury sustained while riding high speed transportation with blunt object trauma of the abdomen more frequent than penetration. However, pedestrians and heavy industry provide certain instances of abdominal wall transgression, while the hunting seasons, the temperament, home, or social life and employment of some citizens keep physicians aware of these problems. The surgeon himself may on occasion suddenly and inadvertently find himself on the inside of the bowel looking out. Of 175 fecal fistulae seen at the University of Michigan Hospital, 22.3 per cent, or 39 cases, were due to surgical trauma. Twenty of these were in various

From The Surgical Service,
U. S. Veterans Administration Central Office,
Washington, D. C.
Read at The Annual Meething of the Puerto Rico Medical Association, November 12, 1965.

portions of the colon. The injection treatment of hemorrhoids at a local institute for colon therapy has recently provided the necessity of diversion colostomy in one patient. In recent years one is increasingly impressed with the late bowel damaging effects of well intended and often cancer-curative pelvic radiation therapy. Therapeutic maneuvers, even in the hands of experienced physicians must be recognized as potent sources of bowel trauma.

Colostomy for bowel trauma is not a recent development. In 1795 Danguesceau exteriorized the proximal bowel in a patient who had driven a wooden stick into the left quadrant of the abdomen in a fall from a wagon. The patient recovered, living for 24 years and dying at the age of 81. Not at all incidentally Danguesceau adapted a leather bag to the bowel opening he had created, thereby introducing the first colostomy bag.

Colostomy and treatment of penetrating wounds of the bowel came into its own in World War II where it was found that the 45 per cent mortality of abdominal perforating wounds in the conflict of 1918 was reduced to 15 to 20 per cent. The greatest single factor in this advance was adherence to the Surgeon General's directive in his Circular 178 of October 23, 1943, demanding the general use in front line hospitals of exteriorization by diversion types of colostomy for wounds of the colon and rectum. "Early operation" was considered to be within 6 to 12 hours of the injury, and is a major factor in success.

In general, perforating lesions of the right colon recover well when either sutured primarily or exteriorized as initial treatment, but if not treated by one of these methods are certain to lead to prolonged and severe complications or death. The fluid fecal stream of the right colon seems to demand less opening for diversion or decompression, hence there are some advocates of appendicostomy for these purposes. However, full colostomy is essential to obviate fulminating infection from perforating lesions in the distal bowel or rectum.

In the less mobile areas of the right colon, single or multiple clean perforations without loss of bowel wall substance are often better sutured primarily and left in place rather than attempting to free attachments • for bowel exteriorization. A simple pursestring similar to inversion of the appendiceal stump is effective, or some operators prefer several interrupted nonabsorbable sutures in the transverse direction of the bowel. It is best to place a double layer of these, or two purse strings, one outside the other. In either case one may consider the wisdom of tacking the closed perforation to the undersurface of the abdominal incision in order that it may, if it reperforates, drain extraperitoneally.

Proximal loop or Mikulicz exteriorization of the ileum or ileocecal region has been a singular contribution, has a place in history, and is rarely indicated today. It creates the problems of an ileostomy with skin excoriation and nutritional imbalances and is, therefore, contraindicated.

In the event that greater injury has occurred to right bowel or surrounding structures, or the patient's condition is precarious, cecum or ascendens perforations

are quickly and easily treated by suturing the perforation to the wound over a catheter as a "nipple" colostomy similar to the formation of a cecostomy. This does not interfere with a normal fecal stream and is simple to close.

Beginning with the hepatic flexure simple or moderate wounds are probably best exteriorized as a loop colostomy, but in massive injury to the right bowel at any point end of ileum to side of colon ileotransverse colostomy is the procedure of choice initially, with intention of reconstructing or resecting the defunctionalized right half of the colon at a later date if this seems indicated. Because of mobility and accessibility transverse colon wounds are more easily treated than other bowel injuries, and those coming to surgery are more often amenable to the lesser procedures. Extensive wounds of the transverse colon are seldom encountered except at autopsy, for concomitant injury of such major vessels as the aorta or vena cava preclude patients with massive injury reaching the hospital. Small transverse colon lesions may be sutured, but the better part of caution is to divert the fecal stream exteriorizing the injured sites to insure against complications from unrecognized additional bowel perforations or breakdown of the original closures. Later formal colostomy closure with adequate preparation and proper selection of time for surgery is most successful.

The solid fecal stream in the left colon is less likely to cause fatal peritonitis than leak of fluid contents from more proximal areas of the bowel. More usual from leaks in the left bowel are localized abscesses and eventually fecal fistulae which may on occasion close spontaneously.

Decendens lesions are usually less easily exteriorized due to anatomic facts of splenic flexure fixation and the short mesentery below. Division of the lateral peritoneal reflection to the mesentery satisfactorily mobilizes the descending portion of bowel. Lesions of this colon segment are often associated with complicating splenic, gastric or other soft tissue and bone injury which may force changes in the general concept of exteriorization of traumatized bowel. However, in cases of extensive trauma the added insult of resection with primary anastomosis may be sufficient to convert the apparently stabilized patient's condition to irreversible shock.

Sigmoid lesions are generally mobile, accessible, and usually easily exteriorized by colostomy.

Rectosigmoid perforations cannot be mobilized and are, therefore, sutured primarily with a diversion colostomy of the upper sigmoid as complementary decompression. The greater danger in rectosigmoid injuries is failure to recognize and treat them. One-third of the surgically initiated fecal fistulae reviewed at the University of Michigan were in the lower sigmoid. It is our firm belief that in present civilian life more fecal fistulae result from surgery than from penetrating external trauma.

Rectal and anal perforations being extraperitoneal are often considered less serious than those of more proximal bowel where peritonitis is a threat. Actually the reverse is true, for without peritoneal protection surrounding tissues are subject to

serious infection which borrows into inaccessible pockets. Resulting peritoneal and pelvic abscesses with fistulae are more permanent than peritonitis, and extremely disabling.

With anal lesions the sphincter mechanism becomes an issue, its permanent loss justifying abdominal colostomy in preference to a less accessible patulous perineal outlet. Urethral and bladder injuries are reasonably frequent accompaniment of anal damage. All rectal and anal perforations require adherence to the same surgical principles utilized in treating bowel injuries above, to reiterate: 1) complete definition of extent of the injury; 2) immediate repair of damaged structures, or their preparation for later repair; 3) and diversion of the fecal stream.

Actual creation of a colostomy is not a difficult technique, although in cases of trauma the operation may be rendered somewhat more complicated by abdominal wall, bowel, or other injuries. Standardization of techniques and attention to the many essential details of preoperative preparation and pos-operative care is impossible because of wide variation in training and ability of surgeons and the multiplicity of situations in which they work.

Any surgical treatment of bowel perforation is predicated on the operator's certain knowledge that circulation to the part is unimpaired. Thereafter, anatomical considerations of mobility and blood supply, and to a certain extent bowel physiology, determine the choice of operation. In the sorely injured the least operation which will be effective in the saving of life and preparation for later necessary correction is the procedure of choice.

The so-called "nipple" colostomy employing a mushroom catheter as mentioned above for selected right colon lesions is similar to cecostomy or appendicostomy.

The spur, (Bloch, Paul, or Mikulicz) colostomy has been abandoned by most surgeons. Its performance prolongs the operative procedure; the septa or spurs are rarely actually firmly adherent or closely approximated allowing frequent interposition of colon, mesentery or small bowel between the limbs; small intestinal loops become twisted around the spurs ;or on closure incompletely crushed septa provide an inverted V or U shaped angulation and sharp narrowing of the bowel. One generally finds it necessary to resect the colostomy and close it end to end. If these considerations are insufficient to condemn the procedure, comparison of hospital stays reveals the spur (Mikulicz) colostomy requires 2½ times the hospitalization period requisite for more protracted operative maneuvers.

Creation of a simple loop colostomy with skin, or fascial and skin bridge, is swift, simple and effective, generates little blood loss, and a minimum of operative or anesthetic trauma. It is accompanied by few complications.

A transverse incision is preferable, transecting the rectus muscle if access to the abdominal cavity is desired for exploration, but eventually aiming at placement of the functioning loop of the colostomy in the angle formed by the vertical fibers of the rectus abdominis muscle and the

flat more transverse musculature laterally.

The most mobile loop of selected or injured bowel is freed of appendages over a segment of 10 cm., a rent is created in an avascular portion of the mesentery, bleeders are secured, and with Penrose drain or moist gauze traction, and occasional manual manipulation, a sufficient loop is drawn outside the abdomen. Of utmost importance is avoidance of tension of the loop, for this endangers blood supply and threatens retraction of the bowel opening below skin level with infection of the abdominal wall or peritoneal surfaces.

The skin, or skin and fascial bridge is created some 2 to 3 cm. in length and widening from 1½ cm. at the free tip to 2 to 3 cm. at the base. This is passed through the rent in the mesentery of the exteriorized bowel loop and sutured to the opposite edge of the wound, ends of the sutures being left long enough to be easily found when removal is attempted in 7 - 8 days. Over this bridge a glass or plastic rod is placed to further support the loop of bowel. It is best to protect its ends with a suitable length of flexible tubing or the tubing itself may be used as a support if sufficiently firm material is available. Thereafter the celiotomy wound is closed from either end until either limb of the exteriorized loop is held snugly but not tightly by the abdominal wall. A simple guide is that one finger can be inserted snugly alongside the bowel through the layers of the abdominal wall, including the peritoneum. It is not necessary to suture the bowel or its appendages to the abdominal wall. It is important to insure when this is an exteriorizing colostomy that all sites of colon trauma are completely outside the abdomen and the abdominal wall.

Initially, opening of the colostomy is requisite only for escape of gas, allowing adherence of the bowel to the wound before releasing the fecal stream on the abdominal wall. Insertion of a catheter through a purse string similar to the cecostomy procedure described is adequate for this early decompression. Later the colostomy may be opened transversely in order to parallel the blood supply and simplify later end-to-end closure. This later opening can usually be done in the treatment room without anesthesia. Use of the cutting cautery is helpful, although odor and noise, as well as the idea, may alarm some patients.

In the dressing it is desirable to wind an opened gauze flat about the exteriorized colon at the skin edges of the wound, and beneath the ends of the supporting glass rod or rubber tubing. A single layer of vaseline gauze mesh is sufficient to keep dressings from sticking to the bowel. Fluffed gauze covers the area, with care in its taping to avoid pressure sufficient to obstruct the exteriorized bowel.

Postoperatively, gastric and small bowel decompression by Miller Abbott and Levine tubes attached to Wangansteen suction is sometimes a useful adjunct until the colostomy is opened. It is not always requisite.

Antibiotics are deserving of mention. It will be noted these have been placed last in consideration for they cannot replace or substitute for exercise of proper surgical principles. Tests of sensitivity of involved organisms should be done to per-

mit choice of proper antibiotics.

It should be obvious that improvement in results from surgery of bowel injury have come not alone with advances in training of surgeons, establishment of facilities, and improvement in anesthesia, but specifically from properly stabilizing patients preoperatively, careful bowel decompression, better control of the fecal stream, and decrease in bacterial contamination. Earlier operation by better trained men in more adequate situations, utilizing more specific supportive measures, including antibiotics, doubtless will permit many colon wounds to be closed primarily. However, the principle of exteriorization of perforating wounds of the colon, or diversion of feces through a proximal colostomy when the injured area cannot be exteriorized is now so established that it should only be abandoned when future experience demonstrates that this can be done with no increase in patient morbidity or mortality. Where all modern improvements are not readily available, even the most skilled of surgeons, must accept effective lesser surgical procedures or staged operations, or his patient with bowel injury will suffer the now inexcusable mortality of this injury as occurred in earlier decades.

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TWO UNUSUAL X-RAY CASES

Laszlo Ehrlich, M. D.

It happens, not infrequently, that one comes across an unusual X-ray finding consisting of a variant of an abnormal morphology. For instance, a mediastinal mass may appear as a fairly obvious case of teratoid tumor and turns out to be an aortic aneurysm. This could be called an unusual case of the "garden variety". There is, however, another type of unusual case which the radiologist has never seen before, and most probably will never see again. It is so rare that it may not be mentioned or described in the textbooks.

We have had two such cases last year; they will be presented to you in order to share the experience.



Fig. 1: Case 1

First admission:

A 34 year old white male was transferred from another hospital on July 29, 1963 with complaints of weight loss (25 lb.) and findings of anemia and splenomegaly. Splenic biopsy at that hospital had been non-diagnostic. Transfer diagnoses were:

1. Splenomegaly ,cause undetermined
2. Possible lymphoma

Stools and circumoval test were positive for S. *mansoni*. Hemoglobin, 9 grams/100 ml. Biopsies of the liver, axillary and cervical nodes were negative. Esophagoscopy was negative for varices.

Barium swallow was suggestive of varices (Fig. 1). Patient was discharged on August 23 with a diagnosis of Schistosomiasis, intestinal and hepatosplenic.

Second admission:

Patient was readmitted on October 28, 1963 because of marked weakness and diarrhea. Physical examination was unchanged. Esophagoscopy showed varices. Bone marrow biopsy was non-diagnostic.

Barium swallow was negative for varices. Upper GI series showed marked displacement of the stomach by splenomegaly, possibly neoplastic (Fig. 2 and 3). Intravenous pyelogram showed caudad displacement of the left kidney by the enlarged spleen; otherwise negative (Fig. 4).

Patient was discharged on December 3 with diagnoses of:

1. Hypochromic anemia, cause undetermined
2. Esophageal varices
3. Schistosomiasis, intestinal and hepatosplenic.

Third admission:

From the X-Ray Service, Veterans Administration Hospital, San Juan, Puerto Rico. Presented at the Annual Meeting of the Puerto Rico Medical Association, November 12, 1965.



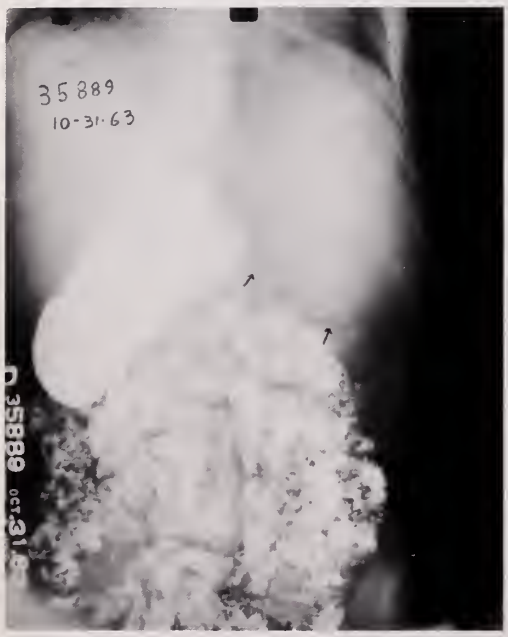


Fig. 2 and *3*: Case 1

Patient was readmitted because of persistent anemia. His appetite was good and he had lost no further weight since last admission. Physical examination was unchanged. Hemoglobin, 9.8 grams/100 ml. Stools were negative for ova and parasites. All other tests were also negative.

Splenoportography: Bizarre configuration of vessels at the site of injection suggesting neoplastic involvement; no evidence of portal obstruction (Fig. 5).

Splenic pulp pressure was 43 cm of water. Laparotomy on February 3, 1964 revealed a large splenic tumor, normal liver and no intra-abdominal lymphadenopathy.

Pathological report: Malignant anaplastic Lymphoma, primary, spleen (Fig. 6).

Comment:

Tumor-like enlargement of the spleen is usually caused by a cyst or an abscess. Primary tumors of the spleen, benign or malignant, are rare. They can arise from lymph or blood vessels, connective tissue, smooth muscle or embryonic rests. Among the malignant tumors, the lymphosarcoma is considered the most common. Although it can grow to a large size, the symptoms can be relatively mild such as it was in our case. After having been weak for about nine months, he regained his appetite, thus stopped losing weight. This indicates that the usual course of generalization of the lymphosarcoma did not take place in our case. The presence of schistosoma ova in the stools explained splenomegaly; all biopsies, including that of the spleen, failed to confirm the initial clinical impression of lymphoma which was suspected already in the contract hospital at the very onset of the disease. The unusual type of splenic enlargement, involving only the upper pole



Fig. 4: Case 1

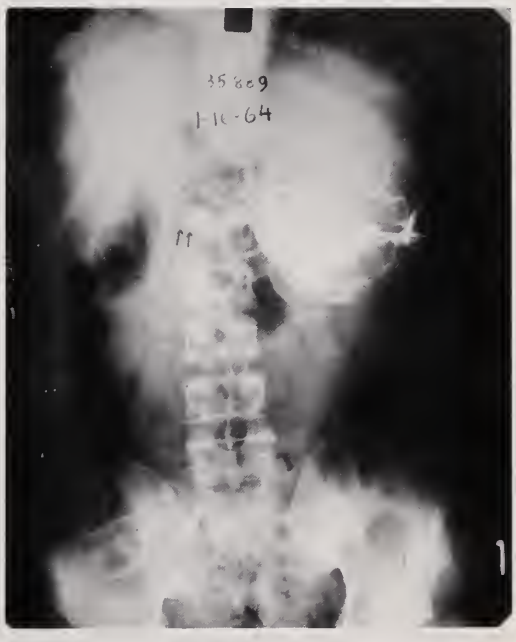


Fig. 5: Case 1

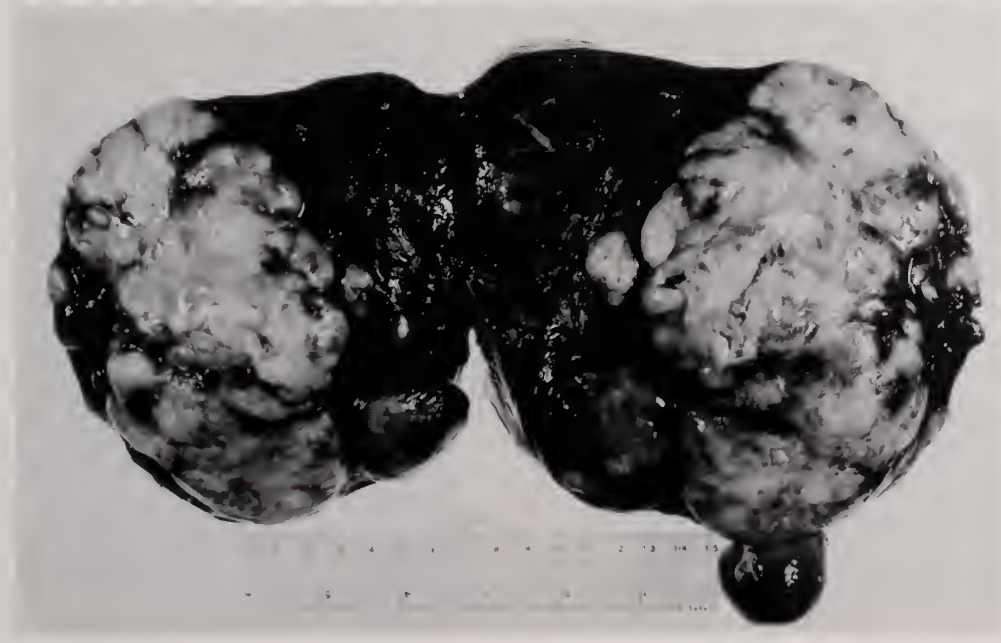


Fig. 6: Case 1

and the bizarre appearance of the splenoportography, however, were pointing toward something unusual, possibly neoplastic. I have carefully searched the literature for a previous report of neoplastic involvement of the spleen diagnosed by splenoportography and found none.

CASE 2:

A 58 year old male was admitted on August 11, 1964 with complaints of weight loss and jaundice of three weeks duration and persistent vomiting during the last week. Examination revealed hepatomegaly and palpable gall bladder. Bilirubin, 14 mg. Alkaline phosphatase, 25 SJR units. Stool guaiac, 2+. Blood counts, normal.

X-Ray Studies: Abdomen (Sept. 22, 1964)—Hugely dilated stomach presumably due to obstruction. Emphysema of the wall of the stomach (Fig. 7). Abdomen (Sept. 23, 1964)—The stomach is smaller, still showing air in its wall and also in the proximal duodenum (Fig. 8). Upper GI. (Sept. 23, 1964)—Extrinsic pressure on post-bulbar segment of duodenum, either due to enlarged gall bladder or dilated common duct (Fig. 9). Abdomen, 48 hr. offlow-up. (Sept. 25, 1964)—No air in the wall of the stomach (Fig. 10). Operation, (Sept. 29, 1964) - Carcenoma of pancreas (head). Large gall bladder.

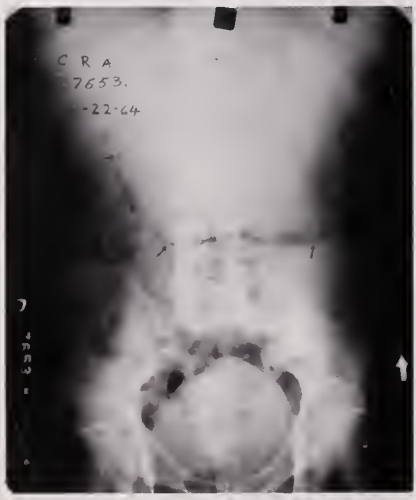


Fig. 7: Case 2



Fig. 8: Case 2

Comment:

Interstitial gastric emphysema must be a rare condition since only six cases have been reported in the literature (Table 1). The first report came from the United States by Canselmo in 1954 (2) and the other five from England (3-7). The present case from Puerto Rico brings the total number of interstitial gastric emphysema to seven.

In all these cases the stomach was markedly distended due to an obstructive process, usually malignant. The case reported by Kay-Butler (5) from England which showed a remarkably similar X-ray appearance to ours, was also due to carcinoma of the pancreas.

The fact that in each case the patient's



Fig. 9: Case 2

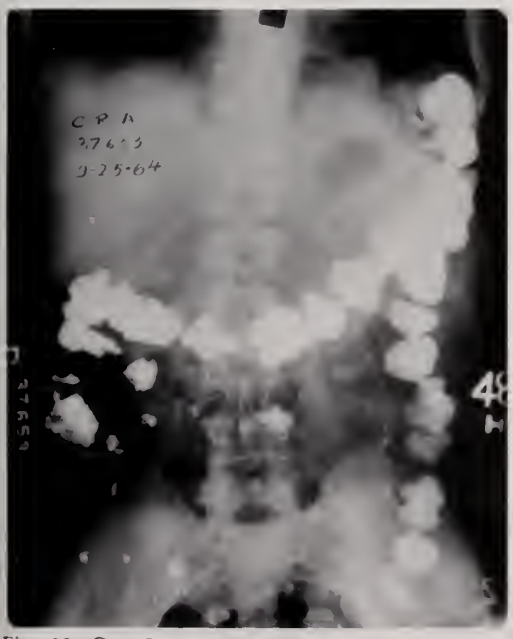


Fig. 10: Case 2

history was characterized by persistent vomiting from several days to several weeks is also noteworthy; it may be the clue to explain pathogenesis of the interstitial gastric emphysema. It is plausible that in a distended stomach with impaired (edematous) mucosa, the continuous vomiting may tear it, allowing the air to enter into the wall. The air usually disappears spontaneously, as soon as the stomach distention subsides.

I must confess that I was rather baffled by the X-ray appearance at the time and some credit is due to Dr. Alfred Axtmayer who happened to pass by and asked me "what is air doing in the wall of that stomach "

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TABLE I: CASES OF INTERSTITIAL GASTRIC EMPHYSEMA

Author	*Year*	*Patients Age (Yrs.)*	*Clinical Diagnosis*	*Duration of Vomiting (Days)*	*X-Ray Findings*
Calselmo (2) (USA)	1954	71	Carcinoma, esophagus	8	Dilated stomach and air in its wall.
Ward (3) (England)	1960	70	Carcinoma, stomach	35	Same
Lumsden (4) (England)	1960	83	Carcinoma, stomach	21	Same
Kay-Butler (5) (England)	1962	52	Carcinoma, pancreas	14	Same
Schorr (6) (England)	1962	75	Gall blader ileus	3	Same
Colquhoun (7) (England)	1964	81	Volvulus, stomach	6	Same
Ehrlich (Puerto Rico)	1964	58	Carcinoma, pancreas	7	Same

Summary

Two unusual X-ray cases were presented. One was a neoplasm of the spleen, primary lymphosarcoma, suggested by splenoportography. The second one was a rare condition due to interstitial gastric emphysema, this being the seventh case reported in the literature.

Resumen

Se presentan dos casos poco corrientes de rayos X. Uno era un neoplasma del bazo, linfosarcoma primario, sugerido por esplenoportografía. El segundo era una rara condición debida a enfisema gástrico intersticial, siendo éste el séptimo caso encontrado en la literatura.

FATAL BALANTIDIAL COLITIS

P. H. García-Pont, M. D.
G. Ramírez de Arellano, M. D.

Balantidium coli is a cosmopolitan ciliated protozoan intestinal parasite of very low incidence (1, 2) that infects man incidentally, the hog being the usual definitive host. Reports of this disease are not found frequently in the American literature. With modern transportation facilities, its occurrence in the human is no longer limited to areas where hogs are heavily infected. The following report is one of a case of fatal balantidiasis with perforation of the colon in a Puerto Rican farmer, and the utilization of a method of treatment not known to be reported in the literature: colonic irrigation with a 1% solution of carbarsone U.S.P. through a proximal transverse colostomy.

Case Report

A 78 year old Puerto Rican farmer was admitted on May 29, 1963 in a clouded mental state, acutely ill, with a two-week history of low abdominal pain, cramps and profuse watery diarrhea. The stools had been blood-streaked at times. He was known to raise a small number of cattle and pigs. He lived in a farm close to a small town in the mountain section of the island and he had never travelled outside of Puerto Rico.

Physical examination showed an acutely ill, dehydrated elderly male with a blood pressure of 100/70, pulse 88 per minute and temperature 98°F. The abdomen was diffusely tender with some voluntary guarding but no rebound. Peristalsis was hyperactive. There was no hepatosplenomegaly. Rectal examination revealed a grossly irregular rectal wall. Sigmoidoscopic examination revealed multiple dark friable areas of mucosa with bleeding points and ulcerations interposed with areas of white exudate protruding into the bowel lumen. Liquid dark stools flowed out of the endoscopy tube.

Laboratory findings disclosed a hemoglobin of 11.9 grams %; hematocrit, 43%, leukocytes, 10,500/cu mm; neutrophiles, 46%; bands, 45%; lymphocytes, 7%; monocytes, 1%; eosinophiles, 1%. Direct smear from the fresh warm stools showed enormeous numbers of motile trophozoites recognized as *Balantidium coli*. Biopsy from the rectal wall showed the same organisms (Fig. 1). Stool culture for bacteria yielded normal flora. Hookworm ova were also found in the feces.

Treatment was begun with oxytetracycline, 500 mg. orally every four hours on June 1, when the diagnosis was definitely established. On June 2, carbarsone, orally, 0.25 gm, three times a day, was started and oxytetracycline discontinued because of gastric complaints. The diarrhea continued and the patient's condition worsened in spite of the administration of fluids and electrolytes. On June 4, 200 cc of a 1% solution of carbarsone in sodium bicarbonate (3) was started as retention enema twice daily. On June 6, paromomycin, 250

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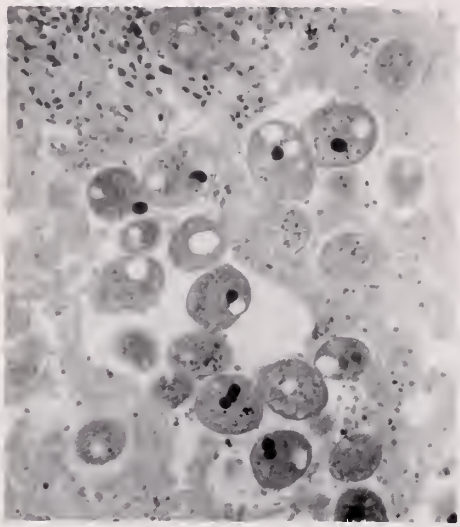


Fig. 1: Many trophozoites of *Balantidium coli* in necrotic area obtained in rectal mucosal biopsy (H&E, X450).

mg four times a day was given in view of the lack of improvement and the report of a leukocyte count of 18,900 per cu. mm. with a marked shift to the left. A distended abdomen was noted that afternoon and a flat plate of the abdomen showed some fluid levels with gaseous distention of the large bowel. The diarrhea had practically disappeared but pain in the left lower abdominal quadrant was prominent. The next day the peristalsis which had been hypoactive was absent to auscultation. Rectosigmoid perforation was suspected and the consulting surgeon advised colostomy, which was done on June 7, 1963. The operative findings included the presence of yellow ascitic fluid and moderate intestinal distention but there was no evidence of generalized peritonitis. A perforation was not found. Right upper quadrant transverse colostomy was performed. Trophozoites were not found in the ascitic fluid.

On June 9, the colostomy was opened. The mucosa was very red but without ulcerations. A biopsy of the mucosa was taken and the histologic section did not show trophozoites. Treatment with oxytetracycline and paromomycin by mouth were continued. On that same day 100 cc of carbarsone solution 1% was first instilled proximally and distally through the colostomy twice daily.

On June 10, the stools were negative for *Balantidium coli* for the first time. Diarrhea was still present. Fever spikes to 101° occurred on several occasions. Intravenous albumin was given. On June 15 tachycardia developed. Dyspnea and high fever followed. Penicillin in high dosages was started. A chest film was negative. The lungs were clear.

On June 19, diarrhea was absent and the patient looked better. A urinary tract infection and a cellulutis of the left leg complicated the clinical course. A blood culture yielded *Proteus mirabilis* sensitive to penicillin. Eleven days later sodium methicillin was started. The carbarsone instillations were discontinued on June 24 after 14 days of treatment. The total treatment included 11 days of twice a day instillations and three days of a single instillation. On June 26, aqueous penicillin, 4 million units every 4 hours, was started intravenously. Five days later the patient was jaundiced and very toxic. Klebsiella organisms were cultured from the blood. Kanamycin was started but the patient failed to improve and he expired on June 27, 1963. The stools had been repeatedly negative for *Balantidium* since June 10, 1963.

Autopsy was performed 3 hours after death. The body was that of an elderly jaundiced male, cachectic and dehydrated. The pertinent findings were in the abdominal cavity.

A double barrel colostomy was present in the right upper quadrant. The loops of small intestine were remarkably distended. The peritoneal cavity contained purulent, yellowish fluid. Some of the loops of the small intestine in the pelvic cavity were covered with abundant purulent exudate. There was hyperemia of the serosa of the intestinal loops. Most of the purulent fluid was found in the gutters, between the liver and diaphragm, and in the left upper quadrant. The peritonitis was secondary to a perforation of the anterolateral wall of the cecum. There were no ulcerations of the mucosa of the small intestine. The entire colon was severally affected by an inflammatory process with ulceration of the mucosa. Multiple tags of

mucosa, grossly suggesting pseudopolyps, and edema of the wall and pericolic fat were noted. The rectum and sigmoid showed severe changes. The cecum and ascending colon presented multiple superficial ulcers ranging from 3 mm to 2 cm in diameter. The ulcers were shallow, the edges undetermined, and the base covered with yellowish shaggy exudate. There was complete obstruction by thrombosis of the portal vein, extending from the junction of the splenic and superior mesenteric veins to the intra-hepatic radicals. No abcesses were found in the liver. Histologic sections of the rectum and sigmoid showed complete loss of the intestinal mucosa. The surface was made up of granulation tissue in which mononuclear cells and plasma cells predominated. The inflammatory process extended to the muscularis externa. The base of the ulcers was made of granulation tissue. These lesions failed to show *Balantidium coli* trophozoites in numerous sections examined (Fig. 2). Thrombosis of intrahepatic branches of the portal vein were found with ascending cholangitis and cholestasis. The lungs were edematous and congested. Cultures of the peritoneal exudate were positive for *Klebsiella-Aerobacter, Escherichia coli* and enterococci.

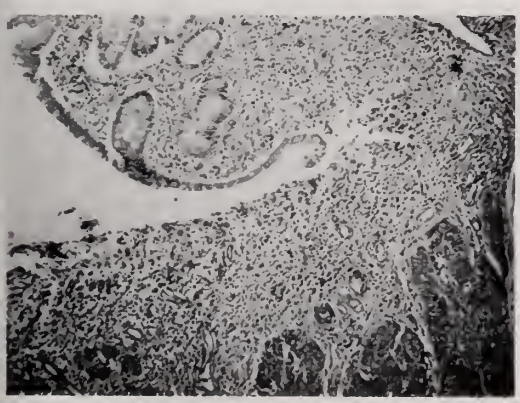
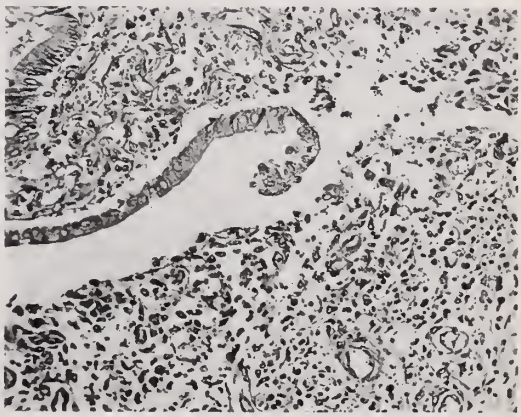


Fig. 2: (A, B) Post mortem histologic section of one of the multiple areas of colonic mucosa, showing ulceration with undermining of epithelial lining and round cell infiltration. No trophozoites were found. (H&E, X350).



Discussion

The patient was treated vigorously with various drugs known to be effective in the treatment of balantidiasis (3, 4, 5, 6). Carbarsone was used orally, by rectal instillation and through a transverse proximal colostomy proximally and distally; at the same time antibiotics were given. Because of this fact the eradication of the parasite cannot be attributed to a single agent or method. Since the area where the *Balantidium coli* inhabits preferentially is the colon (1), close to the cecum, it is possible that colonic irrigation through the colostomy was the most effective way of exterminating the organism. Since the autopsy was performed soon after death, the chance of post-mortem lysis of the Balantidium was considered small. The extensive ulcerations present at admission and later found at necropsy, probably formed the portal of entry of the terminal gram negative bacteremia. Pylephlebitis combined with dehydration served as ground for the portal vein thrombosis and cholan-

gitis that developed. The effect of the medication on the histological appearance of the colonic mucosa or its relation to the perforation cannot be definitely established. The pathological findings were similar to those already known to occur in fatal cases of balantidial colitis without the local instillation of any medication (7; 8, 9, 10).

Since perforation is one of the complications of severe balantidial colitis, if colostomy is performed, (preferably a proximal transverse colostomy), treatment with a 1% solution of carbarsone instilled proximally and distally can be of help in controlling the infestation. Future trial of this method is warranted.

In spite of the low incidence of balantidiasis, similar cases as the one presented can be found anywhere. The incidence of balantidiasis among Puerto Ricans in New York City was reported as 0.6% by Shookhoff in 1947 (5). In Puerto Rico the incidence was calculated in 1946 as 0.2% but other reports have given a lower incidence of 0.08% (8, 11). Difference in incidence have been related to the freshness of the stool specimen examined. We believe that awareness of the

The patient died of perforation of the existence of this condition is important since recognition of the disease at an early stage can prevent fatal complications like the ones developed in our case.

Summary

A case of fatal balantidial colitis with perforation of the colon in a Puerto Rican male is reported. Colonic irrigation with a 1% solution of carbarsone through a proximal transverse colostomy was utilized in the treatment together with antibiotics. Parasite eradication apparently was achieved.
colon with peritonitis and pylephlebitis. Further trial of this technique is suggested. Attention is called to the existence of this disease among Puerto Ricans.

Resumen

Se informa un caso de colitis por *Balantidium coli* con perforación del intestino grueso resultando en muerte del enfermo. Se utilizó como modo de tratamiento la irrigación del colon con una solución al 1% de carbarsona a través de una colostomía proximal en el colon transverso, conjuntamente con antibióticos. Exámenes histológicos demostraron que el parásito fué exterminado. Aunque el paciente falleció de complicaciones, se sugiere este método como una forma de tratamiento a considerarse en el futuro y a someterse a más estudio.

Se llama la atención hacia la existencia de este parásito entre los puertorriqueños.

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CLINICO-PATHOLOGICAL CONFERENCE*

Edited by Dr. Julio V. Rivera

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Clinical Abstract

This 40-year old negro male was admitted on April 27, 1962 with complaint of exertional dyspnea.

In July, 1958 this patient entered a hospital in New York City for the treatment of pulmonary tuberculosis. This diagnosis was based on the finding of a cavity in the right upper lobe, a positive tuberculin test and two positive cultures for tubercle bacilli. He was treated in the hospital with isoniazide and para-amino salicylic acid for about 6 months. He continued this treatment at home.

In 1959 he developed exertional dyspnea, orthopnea, edema of the legs and genitalia and ascites. He denied hemoptysis, fever and chest pain. Heart disease was diagnosed. He was hospitalized repeatedly during the following two years in New York for the treatment of these symptoms. In March, 1962 he came back to Puerto Rico and shortly thereafter entered another hospital from which he was transferred here.

Until 1958 when he went to New York City, patient worked as a sugar-cane cutter. He smoked about 10 cigarettes per day and drank alcohol heavily at times. He had syphilis in 1941 which was treated with Salvarsan and bismuth. An allergic dermatitis occurred. In 1955 he had jaundice for 2 months. No history of rheumatic disease, hypertension, diabetes or kidney disease was elicited. The family history was not relevant.

On admission the patient was found well developed, undernourished and dyspneic. Temperature, 98ºF; blood pressure, 110/90 mm Hg.; pulse, 96/min., regular. There was slight conjunctival icterus. Neck veins were markedly distended. A hepatojugular reflux was elicited. Moist rales were heard at the right apex and both lung bases. The heart was enlarged to the left. A diffuse apex impulse and systolic pulsations at the left third and fourth intercostal space next to the sternum were found. No thrills were felt. A soft grade 2 blowing systolic murmur was heard at the apex at the lower end of the sternum. This murmur was transmitted to the left lung base. At the tricuspid area it increased with inspiration. The heart tones were poorly heard at the base. $P_2 > A_2$. M_1 was faint. Paradoxical pulse was not detected. Ascites was present. The liver was

* *Presented at the Annual Meeting of the Puerto Rico Medical Association on November* 12, 1965.

felt 6 cm below the costal margin. The spleen was not felt. There was moderate leg edema and there was clubbing of the fingers. The skin was normal. Neurological examination was negative. The testes were atrophic.

Arm-to-tongue circulation time (Decholin) was 55 seconds. Venous pressure was 31 cm of water.

Cardiolipin complement fixation was weakly reactive. Hemoglobin, 13.2 g/100 ml; leukocytes, 9,400/cu. mm. Urine acid, sp. g. 1015; negative glucose, albumin and sediment. Urea nitrogen, 9.6 mg %; total protein, 7.7 g %; albumin, 3.8 g %; sodium, 151 mEq/L; potassium, 4.2 mEq/L; chloride, 106 mEq/L; CO_2, 28 mEq/L. Bilirubin 1.5 mg total, 0.35 mg direct. Thymol turbidity, 4.5 units. Prothrombin time, 13 sec. Glutamic oxalacetic transaminase (SGOT), 35 units; glutamic pyruvic transaminase (SGPT), 14 units. Alkaline phosphatase, 12 units. Circumoval test for Schistosoma was negative. Serum protein electrophoresis: albumin, 55%. $_1$, 3.6; $_2$, 9.3; *B*, 14.3; *Y*, 17.9. LE preparation was negative. BSP, 23% retention in 45 minutes.

Chest X-ray (Fig. 1) showed clear lung fields except for fibroid changes at the right upper lobe. The heart was enlarged, globular in shape, the aortic knob was small and the pulmonary conus prominent. Cardiac fluoroscopy showed normal pulsation, posterior displacement of the esophagus by the left atrium and enlargement of all other chambers as well.

Electrocardiogram (Fig. 2) showed complete right bundle branch block (RB-

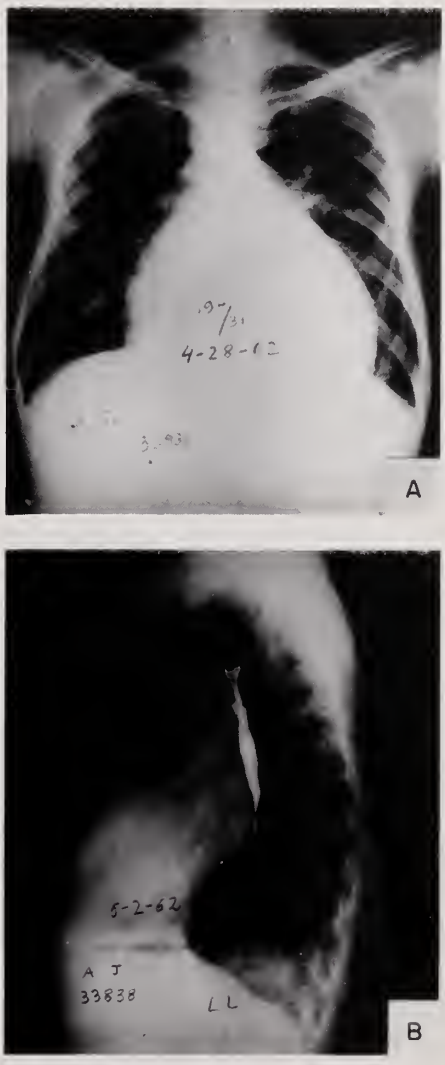
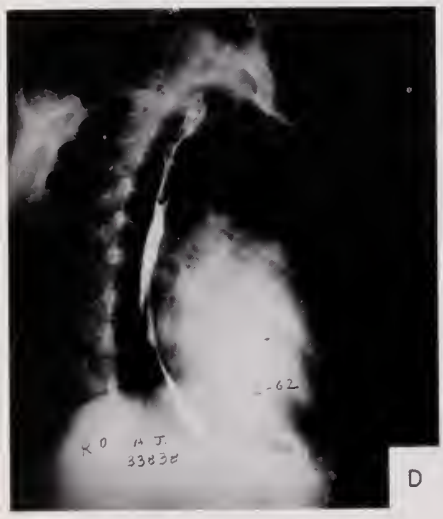


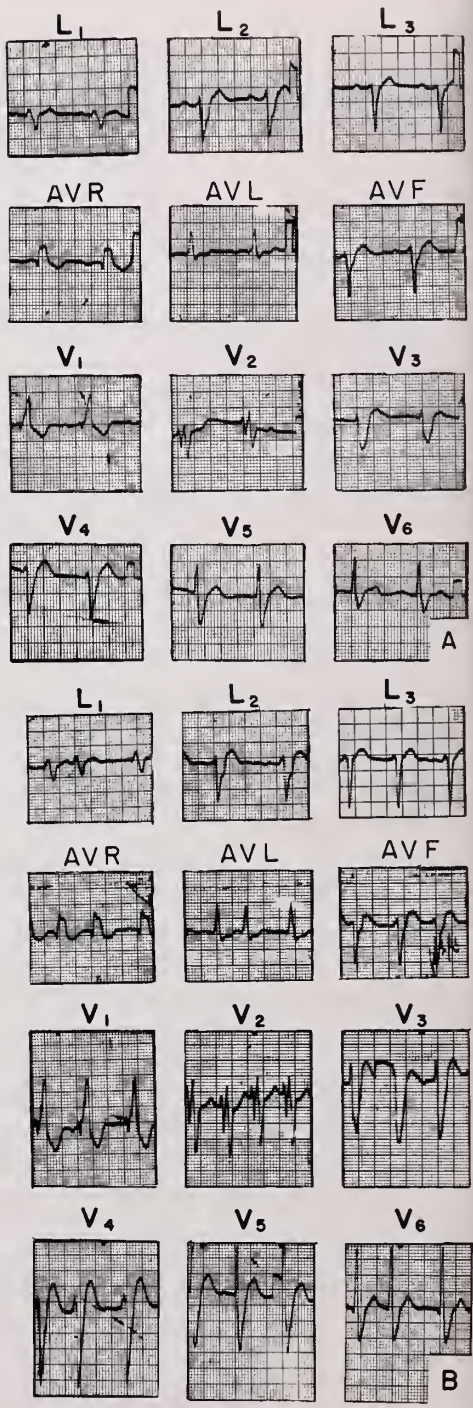
Figure 1:

A. Chest roentgenogram on April 28, 1962 showing enlarged globular heart with small aortic knob and prominent pulmonary conus. Lungs are clear.

B.C.D. Chamber analysis on May 2, 1962 showing enlargement of all chambers. Cardiac pulsations were normal.







gure 2:

A. Electrocardiogram dated April 27, 1962 showing right bundle branck block, left axis deviation and high QRS voltage in the precordial leads.

B. Electrocardiogram on December 25, 1963 shows in addition, atrial fibrillation and premature ventricular beats.

BB) left axis deviation and high QRS voltage in the precordial leads.

While in the hospital the patient remained afebrile. Under treatment with low salt diet, digoxin and diuretics he improved markedly and was discharged on May 17, 1962.

In November 1962, May and August 1963, the patient was readmitted with similar symptomatology. Laboratory, X-ray and electrocardiographic observations did not change significantly. Esophagogram in May 1963 failed to demonstrate varices. Liver biopsy in August showed slight dilatation of the sinusoids and minimal portal fibrosis. Each time improvement occurred but hepatic congestion never disappeared. At home he continued taking chlorothiazide, digoxin and chlormerodrin.

One week prior to the last admission in October 1963 marked painful swelling of the right leg appeared which spread upwards from the ankle to the thigh. The inguinal nodes became painful.

On admission the patient was acutely ill, markedly dyspneic and orthopneic. Temperature, 98.6ºF; blood pressure, 120/80 mm Hg.; pulse, 100/min. Cardiac findings were unchanged except for more marked enlargement. Wheezes and moist rales were heard throughout both lung fields. The liver was enlarged, tender and it showed systolic pulsations. Ascites and venous congestion were present. The right leg was edematous up to the thigh where tenderness was elicited on pressure. Pulses were smaller on this leg than on the left. There was moderate edema of the left leg below the knee. The right inguinal nodes were tender.

Hemoglobin was 10.8 g/100 ml; hematocrit, 33.5%; leukocytes, 8,450/cu. mm. Urine showed 4+ albumin. Serum sodium was 112 mEq/L; potasium, 3.9 mEq/L; chlorides, 89 mEq/L; Co_2, 40 mEq/L.

Chest X-ray and electrocardiographic findings were unchanged.

Under treatment with digitalis, chlorothiazide, chlormerodrin and heparin transient improvement was observed. On November 7, a sudden episode of severe abdominal pain occurred which was accompanied by hypotension, generalized pulmonary congestion and hemoptysis. The electrocardiogram remained unchanged. After 5 hours with hypotension he improved following the administration of aminophylline and Cedilanid. Chest X-ray on November 12 showed no new abnormality. After an intensive course of diuretic therapy was given the patient remained relatively comfortable for about 5 weeks although signs of right ventricular failure persisted. On December 25 he had another episode of severe pulmonary congestion and hypotension. The sputum was noted to be blood streaked. He denied having chest pain. Chest X-ray showed no change. Electrocardiogram showed atrial fibrillation and premature ventricular contractions. During the month of January he continued in failure while receiving alternating courses of various diuretics. The laboratory reported considerable electrolyte disturbance (sodium, 123 mEq/L; potassium, 3.5 mEq/L; chlorides, 86.5 mEq/L; CO_2, 30.6 mEq/

L). On February 4 he awakened with pain in the right upper abdomen which radiated around the costal margin to the back. Hepatic and costovertebral tenderness was found. Blood pressure was 76/0 mm Hg. This episode was followed by anuria for 12 hours. First urinalysis folowing it showed albumin and few hyaline casts but no erythrocytes in the sediment. On February 17 recurrence of painful swelling of the right leg occurred. He again received heparin with improvement. Epigastric pain and vomiting associated with marked hepatogemaly ascites and jaundice became prominent in the following 2 weeks. Laboratory findings about this time were as follows: BUN, 16 mg; bilirubin, 4.6 mg; alkaline phosphatase, 15; SGOT, 190 units; SGPT, 124 units; lactic dehydrogenase, 780 units. He also developed mental confusion and became very restless. On March 31 while at the bath-room he suddenly collapsed and died shortly thereafter.

Clinical Discussion

Dr. Louis A. Soloff*

We are dealing with a 40 year old negro man who came into the hospital complaining of exertional dyspnea. This of course is a cardinal but not pathognomonic symptom of left heart failure. Exertional dyspnea occurs also in pulmonary diseases, in anemias and in disorders of the muscles of the chest wall. But the story is so characteristic that we must think almost immediatedly of some type of left heart failure as the cause of this man's admission in the hospital. The first apparently confusing part is that he had pulmonary tuberculosis four years previously. The diagnosis seems to be undeniable. This raises the question as to whether his cardiac problem or exertional dyspnea could be related to pulmonary tuberculosis. The commonest manifestation of tuberculosis of the cardiovascular system is tuberculosis pericarditis. There are two modes of onset of tuberculous pericarditis. One is the so called conventional or typical type, namely, a person who complains of fatigue, and has a low grade fever with the X-ray showing a huge cardiac silhouette. The onset that occurs more commonly today is entirely different; namely, with severe chest pain which is practically identical with that of so called acute benign pericarditis and may even be mistaken for an acute myocardial infarction. Either onset may be followed by cardiac tamponade, or signs of right heart failure. The apparent onset here is not either one of these two, so that it would seem to me unlikely that this represents tuberculous pericarditis. He came into the hospital in 1959 complaining of severe shortness of breath, orthopnea, exertional dyspnea, edema of the legs, genitalia and ascites. These findings represent, if cardiac, severe right heart failure. This is puzzling because the symptomatology is that of left heart failure yet his signs are those of right heart failure. It will be necessary for me to tie these two together

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to arrive at a single explanation for both. He had no hemoptysis, no fever, no chest pain. He was apparently treated for heart failure and finally came from New York to Puerto Rico.

We have a number of interesting occupational and social habits which enter into the differential diagnosis. The first is that he worked as a sugar cane cutter. I think it will be very foolish for me to discuss illnesses which are associated with the sugar cane industry. I know nothing about them. Probably they form some type of pulmonary fibrosis or bagassosis which could produce right heart failure and dyspnea. He was a smoker and he drank alcohol heavily. The latter is very important and I think it could very well be the cause of his cardiac illness. In recent years it was taught that alcohol does not affect the heart. Actually, over 50 years ago, most internists felt quite certain that alcohol injured the heart. But pathologists over 30 years ago came to the conclusion that alcohol was harmless to the heart. Damage was presumably due to contaminants (copper, etc.) in the stills. However, with the increasing recognition of the frequency of cardiomyopathies of unknown origin, alcohol is again being regarded as harmful to the heart. A history of alcoholism is obtained in up to 80% of some series of cardiomyopathies. We do know that alcohol does constrict coronary arteries, profoundly influences glucose and fatty acid metabolism and may have more fundamental mitochondrial effects.

Alcohol also may produce transient or permanent atrial fibrillation. Transient fibrillation should therefore suggest the possibility of alcoholism as well as thyrotoxicosis. In any huge heart of obscure origin, alcoholism must be considered as a cause and this is of course true in this case. This man also was syphilitic. Syphilis produces primarily a disease of the media of the ascending aorta. Aneurysm, aortic regurgitation and coronary ostium stenosis are complications of this disorder. None of these three explain this man's symptomatology. Neither coronary pain nor signs of aortic regurgitation were present. Nor was there X-ray evidence of aneurysm. Pathological conferences somtimes uncover very rare manifestation of illnesses. It is possible, to have a gumma; to have a tuberculoma, to have a granuloma, or it is even possible to have a tumor of the heart which can affect any region of the heart. Such lesions involving the septum of the heart or wall of the left ventricle, could explain the entire picture. However, because of their rarity, I mention then only as possibilities.

In addition, our patient was allergic. Allergy can produce periarteritis nodosa which can affect the cardiovascular system and produce bizarre symptoms and signs. Also Wegener's granuloma probably of similar origin can affect the heart and the lungs. I think these disorders are unlikely, primarily because of the normal white cell count.

Our patient had jaundice for two months which could be due to allergy, a surgical disorder, to pancreatitis or to alcoholic cirrhosis. Can it be of cardiac origin? Yes. Jaundice is seen in heart disease.

Most commonly it is due to pulmonary infarct with consequent dissolution of the blood particularly in one with liver disease which this man obviously had. The second cause for jaundice is severe, prolonged, congestive heart failure. It is seen particularly in constrictice pericarditis, tricuspid regurgitation, or in any person who has intense liver congestion for a long time. There is a central atrophy and hypoxia which interferes with the disposal of the pigments of the blood.

Now we come to his admission into this hospital. He was well-developed but poorly nourished and short of breath. I emphasize this problem of nutrition again. We sometimes think of malnutrition simply as a problem of not having enough food, food, but this is not necessarily so. The problem is not just getting enough food but being able to use it. A patient who has severe heart disease may not expell sufficient blood to feed his tissues. The patient who has heart failure usually looks well nourished because of fluid retention. Weight loss is a prognostic and diagnostic sign of severe heart disease.

The rales at the right apex do not mean active tuberculosis. Patients who have had tuberculosis of the upper lobes will frequently have rales permanently. This signifies that there is residual bronchiectasis with fluid. It does not signify active tuberculous.

Now we come to the heart. The heart is enlarged more to the left. There is a diffuse apical impulse; there are systolic pulsations at the left third and fourth intercostal spaces next to the sternum. This of course means that the right heart is also enlarged and that it is under pressure or under increased flow. There were no thrills and this is very interesting and important as there is a soft grade 2 blowing systolic murmur which is heard at the apex and the lower end of the sternum. The murmur is transmitted to the left lung base. A murmur which goes way around to the back means mitral regurgitation. It doesn't necessarily mean that there is a organic lesion. We have another murmur at the tricuspid region which increases with inspiration. This represents tricuspid regurgitation. I cannot accept the two murmurs as being of the same origin. The heart tones were poor, P_2 was louder than A_2 which means that there is pulmonary hypertension. The first sound was faint, which is what we'd expect either in mitral regurgitation or in a heart muscle that is severely diseased, and cannot contract with force and therefore does not close forcefully the mitral valve. Paradoxical pulse was not detected. This does not necessarily exclude constrictive pericarditis. If severe congestion is present inspiration may not be able to change the pulse. The heart can't do more than it is doing when severe failure is present. Paradoxical pulse depends upon changing the flow of blood on the right and the left side of the heart. Ascites was present and the liver was markedly enlarged. The spleen was not felt.

This is important because if one were thinking of granuloma, e.g. sarcoid, one would expect the spleen to be involved. We are probably not dealing with any systemic

granuloma with a lesion in the left ventricle or the septum of the heart. There was edema and clubbing of the fingers. Clubbing can be congenital. It is very important whenever one sees clubbing to ask the patient whether his fingers were always so shaped. If clubbing occurred during the patient's illness, one should think of outstanding causes such as sub-acute bacterial endocarditis, congenital heart disease associated with cyanosis and polycythemia, in various types of intestinal and pulmonary diseases and in cirrhosis of the liver. Sub-acute bacterial endocarditis is unlikely as is congenital heart disease. I wonder whether the clubbing is related to his basic disorder. The circulation times are considerably prolonged, which verifies the presence of failure on the right side as does the elevated venous pressure.

He had a positive test for syphilis, stigma of his previous clinical syphilis. His blood count is unusually good which excludes congenital heart disease with right to left shunt. He has a normal urea nitrogen; the protein is perhaps slightly abnormal; the A/G ratio is slightly abnormal which could fit in with liver disease; his sodium is high normal, potassium is normal. I should like to emphasize the fact that when you're dealing with cardiac and pulmonary diseases, we should no longer measure CO_2 content or CO_2 combining power. These can be normal because the spread of normal is so great. What we want to know really is the pressure under which the carbon dioxide is present in the blood the Pco_2 and the pH. These today are a very simple test. Pco_2 is most informative in separating cardiac from pulmonary disease and pH for diagnosing acidosis or alkalosis. The liver functional tests were not too important. LE preparation was negative.

Now we come to the chest X-rays. The heart is tremendously enlarged. I certainly would feel that the right atrium and right ventricle are involved; the left ventricle probably is, but we'll tell better on the oblique or lateral views. We notice that we can hardly see the aorta. This is important because this means that there is either disease in the ventricular muscle wall or that part of the blood from the left ventricle is going away from the aorta. The second thing that we see here is the vascular markings in the hilar region, a sign of pulmonary venous congestion. I see very little actually in the parenchyma of the lungs. There are strands in the right apex which represent his old tuberculosis. The esophagus shows a little curvature backwards; not as much as I thought from reading the summary. I can't say that this is really excessive. We see a pulmonary artery bulge above here. In the left oblique view there is enlargement of the left ventricle. The left ventricle overlies the spine. Occasionally, when there is a huge right ventricle, the heart can be pushed backwards so that the heart overlays the spine even though the left ventricle is not enlarged. I think there is enlargement of the left ventricle and also enlargement of the right ventricle which flush up against the anterior chest wall in the right oblique

position. There is marked enlargement of all the chambers. In 1963 the heart is still larger and hilar markings are increased. I get the impression here that the right atrium is now bulging. Its border is very convex. I think the right atrium is getting under more and more pressure. And again we can see the enlarged pulmonary conus and a small aorta. From the X-ray standpoint I think there is enlargement of all chambers, but not as much enlargement of the left atrium as I assumed from reading the case summary.

Now we come to the electrocardiogram. This is a very disturbing electrocardiogram. It shows a right bundle branch block. You can see it very nicely in V_1. There is a sinus rhythm. There is an initial upwards deflection in lead 1 and 2 and there is a very marked left axis deviation. This is not the type of picture that is seen in isolated right heart enlargement. A picture of this sort makes me feel that there should be some involvement of the left ventricle. I have seen such ventricular complexes in myocardial infarction of the left ventricle and the septum. The history certainly does not tell us that there is any infarction. There has been no pain at any time in spite of the severe disease. This is not the type of picture we ordinarily see in the myocardiopathy, although it could be. As a rule, in myocardiopathy the R waves are not quite as tall. Equally important is the normally written T waves in one with severe heart failure and under digitalization. This is the type of picture that one may see in congenital heart disease. One which by itself suggests an atrial septum primum. In other words, a patient who has a hole in the atrium and has either a secundum type with mitral cleft, a little separation of the mitral leaflets or an atrial primum has a severe left axis deviation written counterclockwise and a right bundle branch block. We can also see this in the common septal defect involving both the atria and the ventricles at the base. The one disturbing feature for this diagnosis is the absence of a grade 5 or 6 murmur. At any rate, from the ECG standpoint I put high up on the list an atrial septum defect of the secundum type with a mitral cleft or a primum type of atrial septum or common atrioventricular canal. Contrary to usual statements, many of our patients do not have recognizable phlethora of the lungs, even when the shunt is large. Our patient went along and developed painful swelling of the right leg. He obviously had some type of thrombophlebitis with infection in the inguinal lymph nodes. He became acutely ill, and markedly dyspneic. His cardiac findings were unchanged except for increasing cardiomegaly. He developed wheezes, and rales were heard throughout the lung fields. The liver was enlarged and became tender. He had systolic pulsations, a sign of tricuspid regurgitation. His right leg became more edematous. I think this is thrombophlebitis probably not directly connected with the heart except on the basis of congestion. He did develop an anemia, 10 grams of hemoglobin, and he had electrolyte disturbances with a very marked drop in his sodium. We notice now

that the CO_2 combining power is 40 mEq per liter. Again, may I say this is not really what we would want to know but it does suggest that he had some difficulty in removing carbon dioxide from his lungs and I would suspect that there was significant pulmonary disease in addition to whatever his cardiac disease was.

He was treated from the cardiac standpoint and apparently recovered and felt well for 5 weeks though right heart failure persisted. He developed an episode of severe pulmonary congestion and hypotension and sputum which was blood streaked. I would suppose that he had a pulmonary infarct which came from his thrombophlebitis. He, however, did not have chest pain and nothing new was seen in the X-ray which of course is disturbing but does not exclude this diagnosis. He continued to have failure and electrolyte disturbances.

Then, one day he was awakened with pain on the right upper quadrant with radiation around the costal margin to the back. This suggests that he had some renal problem, I suspect a renal infarct. If present, how could it get there? This of course, could be simply an extension of his thrombophlebitis up through the inferior vena cava or could be an arterial embolus. If it were an arterial one, we think of paradoxical embolization. If he really had a hole in his septum increased pulmonary pressure would carry the thrombus through the hole into the arterial side. He did have findings in his urine but unfortunately for this type of diagnosis, he had no red cells in his urine. He then developed painful leg swelling. He was treated with anticoagulants. His jaundice became more prominent which does not surprise us, of course. He developed elevations of all of his enzyme which could be on the basis of liver disease; and then he finally died.

I think there are many possible causes for his illness. If I had to choose one other than these unusual granulomata involving the heart, or tumors, and as I say, I don't believe there is a cardiomyopathy, I don't believe that it's a myocardial infarction; I would feel, based primarily on the electrocardiogram, upon the fact that we have quite clear-cut evidence of right heart failure, and a patient who has a big left heart and symptoms, the fact that he had developed abdominal pains which could be arterial embolization, I would feel that perhaps the most likely explanation for this very bizarre group of symptoms and all the other illnesses he had, would be congenital heart disease with an atrium septum secundum with a mitral (and tricuspid) cleft. Other possible anomalies that could be considered are a primum defect and common atrio-ventricular canal. I would thus put congenital heart disease as my first choice and then in the back of my mind think of granuloma, myocardiopathies and infarction.

I vote against myocardial infarction because of the history and normal T waves and against myocardiopathy (although tempted to do so because of the present popularity of the diagnosis of alcoholic myocardiopathy) because of the normal T waves in one with congestive heart failure and digitalization.

Pathological Discussion

Dr. G. Ramírez de Arellano:**

At the time of autopsy there were approximately 3,000 ml of clear serous fluid in the peritoneal cavity, 300 ml in each pleural space and 250 ml in the pericardial sac. The lower extremities were severly edematous and there was no difference between the right and left. There was no clubbing of the fingers or toes. The heart was remarkably enlarged (760 g) and globular in shape (Fig. 3.). The pericardium showed no evidence of pericarditis. All cardiac chambers were dilated. The endocardium lining the left aspect of the interventricular septum was slightly thickened. The right ventricle showed marked hypertrophy of the papillary muscles and trabeculae carnae. The pulmonary conus was very prominent and the ventricular wall measured 7 mm in thickness which is definite anatomical evidence of pulmonary hypertension. All cardiac valves were grossly normal. There was no evidence of mural thrombosis in any of the cardiac chambers. The coronary arteries were carefully dissected and found to be patent and pliable. The aorta was essentially normal. There was no evidence of a cardiac anomaly.

Histologic sections showed hypertrophy of myocardial fibers, occasional microscopic foci of interstitial fibrosis (Fig. 4) and perivascular round cell infiltration. Sclerosis and narrowing of some small intramyocardial arteries and arterioles were also found (Fig. 5). Perhaps the most significant microscopic change, besides the hypertrophy of the muscle fibers, was the presence of foci of acute necrosis of segments of myocardial fibers, which in some instances were accompanied by early infiltration with neutrophils (Fig. 6). This change is most likely related to the last episode of cardiac failure and the electrolytic imbal-

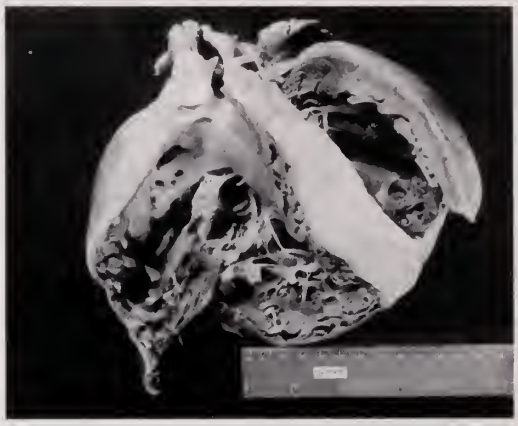


Figure 3: The heart was globular in shape, showing remarkable hypertrophy and dilatation of all chambers.

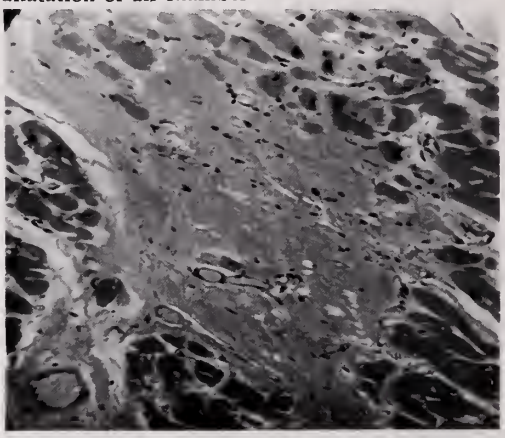


Figure 4: Focal myocardial fibrosis and hypertrophy of myocardial fibers.

** *Assistant Chief, Laboratory Service.*

ance in this case. The microscopic foci of interstitial fibrosis alone do not appear to account for the cardiac disturbance and there is no histologic alteration that would indicate precisely the etiology in this case. A myocarditis must be considered but it is difficult to prove.

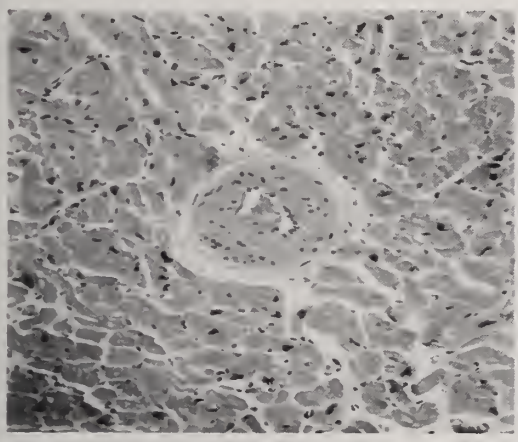


Figure 5: Sclerosis and narrowing of the lumen of small intramyocardial arteries.



Figure 6: Acute focal myocardial necrosis and early leukocytic infiltration.

The gross appearance of the lungs was that of severe chronic passive congestion. Histologically, the alveoli contained numerous heart failure cells. The only other significant histologic change in the lungs was that of sclerosis of small pulmonary arteries and arterioles. There was no evidence of pulmonary embolization either grossly or microscopically. The apex of the right lower lobe showed focal dilatation of bronchioles and interstitial fibrosis without evidence of active pulmonary tuberculosis.

The liver was enlarged secondary to severe chronic passive congestion and histologically there was central necrosis and in areas enough alteration of the lobular pattern and fibrosis to make a diagnosis of early cardiac cirrhosis.

Anatomical Diagnoses:

1. *Primary myocardial disease, etiology (?)*
2. *Cardiac hypertrophy and dilatation*
3. *Chronic congestive heart failure*

Dr. Soloff:

I did emphasize the importance of considering alcoholic myocardiopathy in any alcoholic with a huge heart of otherwise obscure origin. I was tempted to confine my discussion to this present day popular subject but I was driven away from

this diagnosis by the normally written T waves in one with severe congestive heart failure and particularly in one who was digitalized. Normally written T waves under such circumstances always makes one consider an hypertrophied but otherwise normal muscle which is struggling against extra-muscular mechanical fault.

I think we are all puzzled and disturbed by the pathologic findings. They are apparently not those of alcoholic myocardiopahty. What is the signal for this type of hypertrophy? Before one looks for an intrinsic myocardial stimulus or a systemic one, one must be certain that mechanical faults are not operating. The mitral and tricuspid valves are three dimensional structural and functional units and one must be certain that they are competent under *in vivo* pressures. It is particularly important to test the chordae tendinae for their adequacy in so called parachute deformities of the AV valves.

EDITORIAL

A NEW VETERANS HOSPITAL

The demand for hospital beds in Puerto Rico has always been much larger than the supply. The economic structure of the island has been such that only a relatively small percentage of the population has been able to pay for complete medical services. The task of taking care of the public needing medical services has, therefore, fallen to a large extent upon the Government. The laws of Congress that give the veterans the benefit of hospitalization and medical care had in mind primarily benefits to service connected or service aggravated conditions. Non-service connected veterans in order to obtain hospitalization must be unable to defray the expenses and a bed must be available in a Veterans' facility. They are not entitled to outpatient services.

At the termination of World War II the 200-bed general medical and surgical hospital operated by the U. S. Navy in the San Patricio area of Río Piedras was turned over to the Veterans Administration for its operation as a Veterans Administration facility. This served to relieve the already taxed Commonwealth facilities that otherwise would have had to hospitalize non-service connected veterans.

This new facility was opened and operated in accordance with the high standards of other Federal hospitals in the mainland. The staff was carefully selected. The chiefs of all services were Board certified. This was also a requisite for all consultants and most of the attending staff. All the highly specialized services were established. Paramedical personnel with the highest qualifications and in sufficient number to operate the 200 beds were carefully selected to support the medical staff.

At present a new 720-bed hospital is being constructed by the Veterans Administration in the Puerto Rico Medical Center complex to take care of most of the needs of the 135,000 veterans in the island. On its completion it will be the most modern and complete hospital in the Veterans Administration system. This new hospital will have a great impact upon medical care in Puerto Rico. It will be the first hospital in the island where total medical care including that for long term diseases such as neuropsychiatric conditions and tuberculosis will be given under one roof. Education and research that have always been foremost in Veterans Administration medicine will be greatly enhanced. The residency program established at the old hospital will be greatly expanded and integrated with that of the other institutions in the Center. Education in paramedical sciences will also be greatly expanded when legislation now before Congress is approved. We will continue to take an active part in the training of medical and paramedical personnel not only from Puerto Rico but also from the other Antilles, Central and South America.

The Veterans Administration motto of: "To Give Medical Services Second to None", shall continue to be upheld.

J. Chaves-Estrada, M. D.



Architect's Drawing of 720 beds Veterans Administration Hospital and Regional Office, San Juan, P. R.

RESUMENES

IN VITRO QUANTITATION OF THE CIRCUMOVAL PRECIPITIN TEST IN INFECTIONS WITH SCHISTOSOMA MANSONI

(Evaluación cuantitativa in vitro de la prueba de precipitación circumoval en infecciones por Schistosoma mansoni).

Marta Cancio, Amina R. de Sala, R. Rodríguez-Molina y Efraín Toro-Goyco

Exp. Parasit. 16: 64, 1965.

Las globulinas séricas que reaccionan débilmente (+ 1) en la prueba de precipitación circumoval para *S. mansoni* fueron concentradas con sulfato de amonia y liofilización. Se demostró que una reacción + 1 es una reacción positiva verdadera ya que al concentrar las globulinas (+ 1) se evidenció una precipitación circumoval de + 3.

De igual forma las globulinas séricas que reaccionan fuertemente (+ 4) se concentraron para evaluar la posibilidad de formación de precipitados más conspicuos. De esta forma la precipitación obtenida no era significativamente mayor que la obtenida con globulina no concentrada de suero que dá una reacción de precipitación de + 4.

Sueros que reaccionan fuertemente (+ 4) se diluyeron para observar los efectos de la dilución del anticuerpo con el grado de precipitación formada. La dilución de los anticuerpos evidenció la formación menos marcada de precipitados, es decir, a mayores diluciones, menor la precipitación obtenida.

En conclusión, la longitud de la precipitación parece ser una medida cuantitativa de la concentración de anticuerpos presente en el suero de animales o humanos infectados con S. mansoni.

F. Jaume-Anselmi

DERMATOMYCOSES IN PUERTO RICO *(Micosis cutáneas en Puerto Rico) Carrión, Arturo L. Arch. Derm. 91: 431, 1965*

En un estudio de las micosis cutáneas en Puerto Rico en un período que incluye los años 1930 al 1949; presenta 839 casos, que evidencian 8 tipos distintos de tiñas ("ringworm"). Tinea pedis es la más abundante, 39% de los casos; seguida de tinea ungium con 24.1% y ésta a su vez fue seguida respectivamente por tinea corporis, 20.5%; tinea capitis, 11.6%; candidiasis, 2.1%; tinea nigra, 1.3%; tinea nodosa con 0.8% y tinea barbae, O.6%.

Los hongos asociados con estas infecciones consistían en las siguientes 11 especies: Trichophyton mentagrophytes, 41.7%; Trubrum, 36.2%; T. Tonsurans, 8.3%; Microsporum canis, 5%; Epidermophyton floccosum, 3.1%; Candida albicans, 2.1%; Cladosporium wernecki, 1.3%; M. gypseum, 1.1%; Piedraia hortai, 0.6% Trichosporum beigelii, 0.2%; y M. audouini, 0.2%.

Esta data está cuidadosamente analizada y evaluada desde diferentes puntos de vista incluyendo comentarios y experiencias personales del autor.

F. Jaume-Anselmi

TENSION MYOSITIS *(Miositis por Tensión) Flax, Herman J. Ind. Med. Surg. 34: 558, 1965.*

Myositis por tensión es resultante de la mecánica corporal inadecuada, músculos debilitados y esfuerzos ocupacionales en individuos emocionalmente inestables. El síntoma principal es dolor muscular, que puede estar localizado o ser referido y a su vez puede incapacitar por completo al paciente. El dolor referido sigue un patrón definido desde áreas desencadenantes bien localizadas, ya sean primarias o secundarias. El tratamiento consiste en asegurarle al paciente que no tiene una enfermedad orgánica; corregir las posiciones viciosas, fortaleciendo los músculos debilitados y mejo-

rando la función articular afectada. Las áreas desencadenantes del dolor pueden ser infiltrados con novocaína al 1% rompiendo el círculo vicioso de dolor. Terapia sintomática no es recomendable y soporte mecánico tampoco es aconsejable. Si los ataráxicos se utilizan en dosis suficiente para producir relajación muscular, los pacientes en su mayoría se quejan de somnolencia. Lo más importante es hacerle ver al paciente con claridad la causa de su condición — el estado de tensión que produce este síndrome psicofisiológico. Al paciente se le debe explicar que una vez haya desarrollado seguridad emocional, esta madurez va a curar sus padecimientos.

F. Jaume-Anselmi

HEPATOMA EN PUERTO RICO (*Liver Cell Carcinoma (Hepatoma) in Puerto Rico*) *Martínez- Maldonado, M., Girod, C. E., Ramírez de Arellano, G., Ramírez, Elí A. J. Dig. Dis. 10: 522, 1965*

Los records clínicos de 26 pacientes con diagnóstico probado de cancer primario del hígado fueron incluídos en este estudio para determinar si la esquistosomiasis de Manson jugaba papel importante en el desarrollo de esta entidad. Todos los casos de los hospitales de la Universidad de Puerto Rico y Administración de Veteranos entre los años 1946 a 1963 fueron considerados. De los 26 casos, 15 fueron a autopsia, encontrándose cirrosis hepática en 12 casos (75%). Fibrosis esquistosómica no fue hallada en ninguno de los casos.

Para determinar cuan significativo era este hallazgo, los records de 50 casos de arteriosclerosis cardíaca fueron revisados para determinar la coexistencia de esta entidad con esquistosomiasis. Siete casos de granulomas esquistosómicos fueron hallados en este último grupo. Esta evidencia es consistente con la prevalencia de esquistosomiasis en Puerto Rico y favorece la ausencia de relación causal entre hepatoma y esquistosomiasis.

M. C. Miranda, M. D.

RELATION OF ARTERIAL BLOOD PRESSURE TO THE TRANSVERSE DIAMETER OF THE HEART IN COMPENSATED HYPERTENSIVE HEART DISEASE (*Relación entre la presión arterial y el diámetro transverso del corazón en la diámetrosiva del corazón compensada). Elí A. Ramírez, M. D., F.A.C.P. Pedro H. García-Pont, M. D., Circulation 31: 542-550, 1965*

Los autores presentan evidencia estadística sacada de un estudio de 535 pacientes hipertensos, de que la presión arterial sistólica correlaciona mejor con el diámetro transverso del corazón, que la presión arterial diastólica. Desde el punto de vista de las complicaciones asociadas a un aumento en este diámetro del corazón, los hallazgos presentados no son consistentes con la importancia que generalmente se le dá a la presión diastólica en la evaluación del estado del corazón del paciente hipertenso. Ambas presiones, sistólica y diastólica, correlacionan pobremente con el diámetro transverso del corazón. Sin embargo, si fuéramos a escoger una presión para evaluar este aspecto particular del corazón en el hipertenso, tendríamos que coger la presión sistólica en lugar de la diastólica. Estos hallazgos están de acuerdo con conceptos fisiológicos que aunan presión sistolica, consumo de oxígeno, mecánica cardiáca, tamaño del corazón. Si una disminución en la distensibilidad de la aorta o cambio en la hemodinamia del corazón representan factores en la patogenia de una presión sistólica alta, pueden ser también factores adversos en la enfermedad hipertensiva.

Como el aumento de tamaño del corazón es un factor pronóstico de importancia en la enfermedad hipertensiva, los hallazgos de este estudio pueden explicar, por lo menos en parte, la asociación entre aumentos progresivos de hipertensión sistólica y una mortalidad mayor, según se ha reportado por otros. De igual manera, la relación entre hipertensión sistólica y el engrandecimiento del corazón parece ser una observación clínica de importancia en el diagnóstico, pronóstico y tratamiento de pacientes hipertensos.

J. Cianchini-Anselmi, M. D.

ANEMIA DUE TO VITAMIN B-12 DEFICIENCY AFTER TREATMENT WITH FOLIC ACID IN TROPICAL SPRUE (*Anemia debido a deficiencia de vitamina B-12 luego de tratamiento con ácido fólico en esprú tropical). Amer. J. Clin, Nutrit. 18: 110, 1966. Julio V. Rivera, M. D., F.A.C.P., F. Rodríguez de la Obra, M. D., M. Martínez-Maldonado, M. D., Aida Fernández, B. S.*

Se presenta un caso de esprú tropical que inicialmente responde a terapia con ácido fólico, pero que más tarde desarrolla una recaída, con anemia megaloblastica, mientras recibe aún 5 mg diarios de esta vitamina. El nivel sanguíneo de ácido fólico aparece normal al mismo tiempo que el de vitamina B-12 se encuentra muy bajo. Terapia subsiguiente con ácido fólico por boca y también parenteral prueba ser inefectiva, persistiendo el carácter megaloblástico de la anemia. Se obtiene una respuesta rápida, sin embargo, cuando se utiliza vitamina B-12 parenteral, a dosis de 2 ug diarios.

Los autores postulan a base de esto que la anemia es causada por una deficiencia de vitamina B-12 inducida por la alterada absorción intestinal, y que persiste a pesar del tratamiento con ácido fólico. Sugieren, por lo tanto, que el mejor tratamiento del esprú tropical debe incluir tanto ácido fólico como vitamina B-12.

J. Cianchini-Anselmi, M. D.

ULTRASOUND TREATMENT OF PERITENDINITIS CALCAREA OF THE SHOULDER. (*Tratamiento ultrasónico de peritendinitis calcárea del hombro) Herman J. Flax, M. D., Sc. D. (Phys. Med.) Amer. J. Phys. Med. 43: 117, 1964.*

En uno de los pocos estudios controlados de la efectividad de la terapia ultrasónica, el autor de este trabajo analiza los resultados de ésta en pacientes con peritendinitis calcárea aguda. A 17 de estos pacientes se les dió un curso de 10 tratamientos con 2 vatios por cm2. Un grupo control de 7 pacientes recibió un curso similar con la máquina puesta a 0 vatios. Ambos grupos recibieron también rayos infrarojos, manipulaciones y ejercicios de fisioterapia. Al terminar este programa, 16 de los 17 pacientes del primer grupo demostraron una marcada mejoría, con disminución o desaparición de las calcificaciones. Sin embargo, del grupo control, 6 de los 7 demostraron idéntica mejoría con disminución o desaparición de las calcificaciones. No se encontró diferencia significativa alguna entre los grupos al estudiar además el grado de amplitud de movimiento que se consiguió en la articulación afectada, ni el tiempo que transcurrió en conseguirse éste. Obviamente, la mejoría conseguida no se puede adscribir a la terapia con ultrasonido y sí a las otras medidas mencionadas o sencillamente a remisión espontánea.

J. Cianchini-Anselmi, M. D.

ABNORMAL IODOPROTEINS IN SERUM: SEPARATION BY GEL FILTRATION. (*Yodoproteínas anormales del suero: Separación por filtración en gel). E. Toro-Goyco and M. Matos J. Clin. Endocrino. & Metab. 25: 916, 1965*

Muestras del suero de 29 pacientes que habían recibido dosis terapéuticas de I-131 fueron fraccionadas por el método de filtración en gel, utilizando para ello columnas de Sephadex G-200. En diez de estos casos se logró identificar tiroglobulina circulante, en cantidades que oscilaban entre 2.0 a 14.7% del total de yodo radioactivo ligado a proteína. En seis más de los casos se encontraron solo indicios de ella, o sea, menos de 1% del yodo ligado a proteína. En cuatro casos más se pudo identificar otra yodoproteína cuyo yodo no era extractable con butanol y cuyas propiedades físicas eran las de globulina 7S. En todos los casos, la mayor parte de la radioactividad se encontró en una yodoproteína de relativo bajo peso molecular (4S o menor). El encontrar diferentes niveles séricos de tiroglobulina en pacientes que habían recibido dosis iguales de radioyodo sugiere que hay variaciones individuales en la sensibilidad del tejido tiroideo a la radiación.

Concluyen los autores, además, que la filtración en gel con Sephadex G-200 es una técnica eficiente y conveniente para la detección de tiroglobulina en el suero y para la separación de tiroglobulina de otras sustancias de peso molecular más bajo que haya en extractos salinos de tiroides.

J. Cianchini-Anselmi, M. D.

NOTICIAS

Locales

BOLETINES VIEJOS

La Asociación Médica de Puerto Rico está interesada en obtener copias de los siguientes números del Boletín:

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1905	" " "	1923	" " "
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1911	" " "	1928	" " "
1912	" " "	1942	" " "
1913	" " "	1943	" " "
1915	" " "	1944	" " "
1917	" " "	1953	abril, junio y agosto
1918	" " "	1956	enero a diciembre
1919	" " "	1957	agosto
1920	" " "	1962	julio

Aquellos miembros de nuestra matrícula que tengan estos volúmenes y deseen donárselos a la Asociación Médica, favor de comunicarse con el Sr. Eulogio Bermúdez Vélez, Secretario de Redacción.

CONGRESO MUNDIAL DE MEDICINA DEL DEPORTE

El Comité Olímpico de Puerto Rico a través de su Presidente, el Sr. Felicio M. Torregrosa, nos informa sobre la celebración del XVI Congreso Mundial de Medicina del Deporte que se celebrará en Hannover, Alemania Occidental, durante los días 12 al 16 de junio de 1966. Cualquier interesado puede obtener mayor información comunicándose con las oficinas centrales de la Asociación Médica de Puerto Rico.

PREMIOS DOME LABORATORIES

Dome Laboratories anteriormente Dome, Chemicals, Inc., de Nueva York ha establecido por intermedio del Colegio Ibero Latinoamericano de Dermatología (CILAD), dos premios de 800 dólares el primero y 400 dólares el segundo para los mejores trabajos originales de investigación no publicados previamente y relativos a algún aspecto fundamental de la dermatología. Se otorgará además diploma y medalla a todos los firmantes de los trabajos premiados.

Los trabajos deben ser escritos en Idioma Español o Portugués.

Los trabajos para optar al premio deben ser presentados al VI Congreso Ibero Latinoamericano de Dermatología.

Este primer concurso se cerrará el 31 de octubre de 1966.

Para informes más detallados sobre las condiciones del concurso, favor de escribir a:

Dr. David Grinspan
Arenales 947 - 2o. A
Buenos Aires, Argentina

DISTRICT POISON CONTROL CENTERS

The following have been designated District Poison Control Centers of Puerto Rico.

1. San Juan Municipal Hospital
   Dr. Osvaldo González Alvarez, Director
   Tel. 724-7002
   Centro Médico, Río Piedras
2. Ponce District Hospital
   Dr. Luis A. Rosario, Director
   Emergency Room
   Tels.: 842-2080; 842-2048
3. Arecibo District Hospital
   Dr. Jesús Rodríguez García, Director
   Tel. 878-3535, Ext. 31

4. Fajardo District Hospital
Dr. Rubén Ramón, Director
Tel. No. 566
5. Aguadilla District Hospital
Dr. Herminio Aluarel, Director
Tel. 791-0200
Dr. Pedro Mendoza, Asst. Director
Tel. 791-0200
Aguadilla District Hospital
Dr. Sidney Kaye
Profesor of Toxicology and
Legal-Medicine
Coordinator for The Health Department.
Institue of Legal-Medicine
Escuela de Medicina, U.P.R.
Tel. 765-0615; 765-4880, Centro Médico
Río Piedras, P.R.

ESTUDIO SOBRE CANCER

El Dr. Isidro Martínez, Director del Registro Central del Cáncer del Departamento de Salud ha recibido un donativo del Instituto Nacional del Cáncer para llevar a cabo un estudio epidemiológico de todos los casos de cáncer del esófago, faringe y cavidad bucal diagnosticado en Puerto Rico durante el año 1966.

Muchos de estos casos son atendidos en hospitales privados y por sus médicos privados. El doctor Martínez solicita la cooperación de todos los médicos autorizando a los entrevistadores que le asisten en este estudio a acercarse a los pacientes.

Junio 15-17. Conferencias por el Dr. Waldo Rich, auspiciadas por la Academia Americana de Práctica General y el Colegio Americano de Obstetricia y Ginecologia, en la Asociación Médica, comenzando a las 8:00 p. m.

Junio 20-23. La Sección de Ortopedia de la Asociación Médica de Puerto Rico auspicia un curso postgraduado en el edificio de la Asociación Médica, comenzando a las 8:00 p. m. todas las noches. El conferenciante será el Dr. William Howe. Información adicional debe solicitarse al Dr. Arturo Cadilla, Presidente de la Sección de Ortopedia, teléfonos 723-4652 y 724-2160.

LECTURES ON BASIC SCIENCE
APPLICATIONS TO CLINICAL MEDICINE

The following series of lectures will be given at the Medical Service Conference Room, Veterans Administration Hospital, San Juan, Puerto Rico, 11:00 a. m. on Tuesdays.

Physicians and students are invited to attend.

May 17. Immunoglobulins and Nuclear Antibodies; Dra. Esther González de Rodríguez.
24. Estudios sobre la Trombocitopenia y Trombocitopatías; Dr. A. A. Cintrón-Rivera.
31. Physiological Basis for Clinical Organ Scanning; Dr. A. L. Rodríguez Rosado.
June 7. Newer Viruses Pathogenic for Man; Dr. Rafael Mariñelarena.
14. Viruses and Neoplastic Disease; Dr. Rafael Mariñelarena.
21. Recent Advances in the Search for Antiviral Substances; Dr. Rafael Mariñelarena.

Nacionales

PSYCHIATRY RESIDENCY

Psychiatry Residency Training available to qualified physicians with licenses to practice in Puerto Rico. This training program is fully accredited for 1, 2, or 3 years of Psychiatry Residency. Training takes place on the 193-bed Psychiatry Service of a 920-bed general Veterans Administration Hospital in metropolitan Boston, Mass. and in 5 university-affiliated Outpatient Clinics for adults and children. Full range of treatment resources offered by excellent full-time, part-time and consultant staff. Starting salary up to $12,510 per year, depending on qualifications and experience. Write: Dr. David M. Holmes, VA Hospital, 150 So. Huntington Avenue, Boston, Mass.

"THE CANCER STORY"

"The Cancer Story," a booklet prepared by the National Cancer Institute for general reader to explain the nature of cancer, how it is diagnosed and treated, and how science is learning more about it has been issued by the Public Health Service.

The 52-page publication is expected to receive wide use in junior and senior high schools as one of several teaching aids produced as collaborative projects by the National Cancer Institute and the National Science Teachers Association. They include a teaching guide, two film strips, and other booklets and visual aids which will be exhibited at the annual convention of the NSTA in New York, April 1 through 5.

All of the teaching aids are based on the book, "Science and Cancer," written for the National Cancer Institute by Dr. Michael B. Shimkin, cancer researcher and teacher at Fels Research Institute, Temple University Medical School. They were designed under the guidance of a committee of teachers headed by Dr. Ralph P. Frazier of Kansas State Teachers College, and scientists of the National Cancer Institute.

"The Cancer Story" is a simplified version of "Science and Cancer" for those who have not studied biology. It introduces essential technical terms but refers the reader to a glossary in the back of the booklet for an explanation of them.

Single copies of "The Cancer Story" may be requested free of charge from the Public Health Service, Washington, D. C. 20201. Copies may be purchased from the Superintendent of Documents, Government Printing Office, Washington, D. C. 20402. The price is 25 cents each, with a discount on quantities over a hundred.

1966 NORMAN A. WELCH, M. D. ESSAY CONTEST ON MEDICAL ETHICS

The American Medical Association, through its Judicial Council, will sponsor a Medical Ethics Essay Contest, open during this academic year to junior and senior students in accredited medical schools in the United States.

The contest, to be known as the Norman A. Welch, M. D. Essay Contest, is another step in the Judicial Council's Expanded Program on Medical Ethics, according to the joint announcement by F. J. L. Blasingame, M. D., AMA's Executive Vice President, and James H. Berge, M. D., Chairman of the Judicial Council.

Cash prizes totaling $1,000, made possible by a special appropriation by the AMA's Board of Trustees, will be awarded to the winning essays. First prize will be $500, second prize $300, and third prize $200.

The contest is being named in honor of the late Norman A. Welch, M. D., a leading figure in American medicine for many years, who died September 3, 1964, while serving as the 118th President of the AMA.

Complete contest rules, as well as suggested essay topics, are available upon written request from the Department of Medical Ethics, American Medical Association, 535 N. Dearborn Street, Chicago, Illinois 60610. They also may be obtained at the offices of the medical school deans.

June 1, 1966, has been set as the deadline for entries in the contest, which the Judicial Council hopes will be continued on an annual basis. Awards in the 1965-66 contest will be announced at the AMA Clinical Convention, in November, 1966.

Judging of the contest will be by a Medical Ethics Essay Contest Committee, composed of prominent physicians, and by members of the Judicial Council.

LEDERLE RESIDENCY SUPPLEMENTS

The American Geriatrics Society today announced the renewal of three $1,800 grants to encounrage resident physicians to devote more time to the study of the medical problems of the aging.

The grants will supplement the salaries paid to resident physicians while they continue their medical education, and are made possible by Lederle Laboratories, a Division of American Cyanamid Company.

The Lederle Residency Supplements will cover the period between 1966 to June 1967. They were inaugurate in 1962.

Application for the grants should be addressed to the Chairman, Fellowship Committee, American Geriatric Society, 10 Columbus Circle, New York, N. Y. 10019. Deadline for applications is June 1, 1966. Announcement of the awardees will be made at the AGS annual meeting June 23-24 at Chicago.

AMERICAN COLLEGE OF PHYSICIANS POST GRADUATE COURSES

May 9-13. INTERNAL MEDICINE IN LIGHT OF RECENT DEVELOPMENTS, Pennsylvania Hospital, Philadelphia, Pa.; Garfield G. Duncan, M. D.; F.A.C.P., and Robert J. Gill, M. D., F.A.C.P., Co-Directors.

May 16-20. PHYSIOLOGICAL ASPECTS OF CARDIOPULMONARY DISEASE,Indiana Univ., Indianapolis, Ind.; John B. Hickman, M. D., F.A.C.P., Director.

May 23-25. NATIONAL TUBERCULOSIS ASSOCIATION. The 1966 Annual Meeting of the American Thoracic Association will be held in San Francisco, California.

June 13-17. ADVANCED PSYCHIATRY FOR INTERNISTS, Baltimore Psychoanalytic Institute, Baltimore, Md.; Ephraim T. Lisansky, M. D. F.A.C.P., Director.

June 15-18. NEUROLOGY FOR THE INTERNIST, Bowman Gray School of Medicine, Winston-Salem, N. C.; James F. Toole, M. D., F.A.C.P., Director.

Symposium on Psychiatry and Neurology
May 19 to 21, 1966

Symposium on *Psychiatry and Neurology: A practical approach.* Mound Park Hospital Foundation, Department of Medical Education of the Mound Park Hospital, Bay Pines V. A. Hospital, Pinellas County Medical Society, University of South Florida Division of Continuing Education, American Academy of General Practice. The Foundation reserves the right to limit registration. Fee $40.00. 18 Accredited Hours by the American Academy of General Practice. Address *Neurology, Mound Park Hospital Foundation, Inc., St. Petersburg, Florida 33701.*

Junio 26-30. Convención Anual de la Asociación Médica Americana, en Chicago.

CARDIOLOGY NINE MONTH TUTORIAL PROGRAM

A nine month tutorial program in *Cardiology,* September 15, 1966 to June 15, 1967, will be offered by the Institute for Cardiopulmonary Diseases. Scripps Clinic and Research Foundation, La Jolla, California. This will be an intensive academic effort covering the field of cardiovascular diseases and is especially designed for the physician. U.S.A. or abroad, who wants an intensive orientation in cardiology. The objective will be to offer training in the broad discipline of academic cardiology: the techniques of teaching, the use of the literature, the preparation of a manuscript, the art of consultation, history taking, the metods of the specialty (auscultation, x ray, fluoroscopy, electro and vectorcardiography, phonocardiography, cardiac catheterization, angiography, pulmonary function studies), the care and use of experimental animals, an introduction to biophysics and statistics, the selection and maintenance of equipment, maintenance of files and records.

Tuition $1,000
For information, write:
Executive Secretary, Institute for Cardio Pulmonary Diseases
Scripps Clinic and Research Foundation
La Jolla, California
A formal program of the American College of Cardiology.

ANNUAL OTOLARYNGOLOGIC ASSEMBLY

October 1 — 7, 1966. *The Annual Otolaryngologic Assembly of 1966* will be held October 1 through 7, 1966, in the new Illinois Eye and Ear Infirmary at the Medical Center, Chicago. The Department of Otolaryngology of the College of Medicine of the University of Illinois offers a condensed postgraduate basic and clinical program

for practicing otolaryngologists under the direction of Doctor Emanuel M. Skolnik. It is designed to bring to specialists current information in medical and surgical otorhinolaryngology.

Interested physicians should direct communications to the mailing address:

Department of Otolaryngology
P. O. Box 6998
Chicago, Illinois 60680

Internacionales

XVI REUNION NACIONAL DE LA SOCIEDAD MEXICANA DE OTORRINOLARINGOLOGIA

La XVI reunión nacional de la Sociedad Mexicana de Otorrinolaringología se efectuará en la ciudad de Guadalajara, Jal., del 1ro. al 5 de mayo de 1966. La organización está a cargo del Dr. Federico Reiuking, Jr.. Presidente, y del Dr. Juan Oberhauser, Secretario.

Para cualquier información puede dirigirse a Doctor Mora 9-10, México I, D. F. o llamar a los teléfonos 12-31-01 y 12-45-85.

PAN PACIFIC SURGICAL ASSOCIATION TENTH CONGRESS

Agosto 20-25, 1966. *Noveno Congreso Internacional de Enfermedades del Tórax.*

The Board of Trustees of the Pan-Pacific Surgical Association announces the dates of the Tenth Congress in Honolulu and the Second Mobile Educational Seminars which travels to countries bordering the Pacific basin.

Part I, the Honolulu portion of the Congress, will convene at the Princess Kaiulani Hotel on September 20, 1966, and continue through September 28.

Part II and III will depart Hawaii on September 28 and travel to Japan and Hong Kong with Part II returning to San Francisco on October 10, in time for the opening of the American College of Surgeons, and Part III continuing on to the Philippines, Thailand, India, Singapore, Australia and New Zealand, returning to Hawaii on November 1, 1966.

The Tenth Congress offers an extensive scientific program presented by more than 450 leading surgeons from the United States and 22 other countries in 12 different specialties: Colon and Anorectal Surgery, General Surgery, Neurosurgery, Obstetrics and Gynecology, Ophtalmology, Otolaryngology, Orthopedics, Plastic Surgery, Thoracic-Cardiovascular Surgery, Urology, Anesthesiology and Radiology. All physicians and surgeons are invited to attend these meetings.

In this space age, diseases are no longer con fined to geographical boundaries and it has become essential for the medical profession everywhere, to share its scientific knowlege and efforts. Therefore, Pan-Pacific with its Mobile Seminars, is expanding its activities in teaching, education and dissemination of knowledge to doctors living in the Pacific rim countries who are unable to partipate in the Honolulu portion of the Scientific Congresses, in exchange for further education and skill in the diseases unique to the Pacific areas. The Pan-Pacific Surgical Association believes, through the vehicle or medium of medicine and surgery, that our greatest contribution to peace and harmony among all men of all nations can be realized.

For futher information, please write: Pan-Pacific Surgical Association, Room 236, Alexander Young Building, Honolulu, Hawaii 96813.

Oct. 23-29, 1966 IX International Cancer Congress, Tokyo, Japan. A charter flight and several group flights are contemplated, thus substantially reducing the cost of transportation. Members of the immediate family of congress participants will be eligible. Anyone interested should communicate with Tirsch Marks, M.D., 435 East 57th Street, New York 22, N. Y.

Instrucciones para los Autores:

El Boletín acepta para su publicación artículos relativos a medicina y cirugía y las ciencias afines. Igualmente acepta artículos especiales y correspondencia que pudiera ser de interés general para la profesión médica.

El artículo, si se aceptara, será con la condición de que se publicará únicamente en esta revista.

Para facilitar la labor de revisión de la Junta Editora y del impresor, se requiere de los autores que sigan las siguientes instrucciones:

a) Los trabajos deberán estar escritos a máquina a doble espacio y por un solo lado de cada página, en duplicado y con amplio margen.

b) En página separada debe incluirse lo siguiente: título (no excediendo de 80 letras y espacios), nombre del autor (es), institución y dirección postal del autor.

c) Artículos referentes a resultados de estudios clínicos o investigaciones de laboratorio deben organizarse bajo los siguientes encabezamientos: (1) introducción, (2) material y métodos, (3) resultados, (4) discusión, (5) resumen (en español e inglés), y (6) referencias.

d) Artículos referentes a estudios de casos aislados deben organizarse en la siguiente forma: (1) introducción, (2) observaciones del caso, (3) discusión, (4) resumen (en español e inglés), (5) referencias.

e) Las tablas, notas al calce y leyendas deben aparecer en hojas separadas.

f) Si un artículo ha sido leído en alguna reunión o congreso, así debe hacerse constar como una nota al calce.

g) Deben usarse los nombres genéricos de los medicamentos. Podrán usarse también los nombres comerciales, entre paréntesis, si así se desea.

h) Se usará con preferencia el sistema métrico de pesos y medidas.

i) Las fotografías y microfotografías se someterán como copias en papel de lustre sin montar. Los dibujos y gráficas deben prepararse a tinta negra y en papel blanco. Todas las ilustraciones deben estar numeradas (números arábigos) e indicar la parte superior de las mismas. Debe escribirse una leyenda para cada ilustración.

j) Las referencias deben ser numeradas sucesivamente de acuerdo con su aparición en el texto. Los siguientes ejemplos pueden servir de modelo:

6. *Koppisch, E.* Pathology of arteriosclerosis. Bol. Asoc. Med. P. Rico 46: 505, 1954. (artículo de revista).
4. *Wintrobe, M. M.* Clinical Hematology, 3rd Ed. Lea and Febiger, Philadelphia, 1952, p. 67. (libro).

Deben usarse solamente las abreviaturas indicadas en el Cumulative Index Medicus que publica la Asociación Médica Americana.

Instructions to Authors:

The Boletín will accept for publication contributions relating to the various areas of medicine surgery and allied medical sciences. Special articles and correspondence on subjects of general interest to physicians will also be accepted. All material is accepted with the understanding that it is to be published solely in this journal.

In order to facilitate review of the article by the Editorial Board and the work of the printer, the authors must conform with the following instructions:

a) The entire manuscript, including legends and references, should be typewritten double-spaced in duplicate with ample margins.

b) A separate title page should include the following: title (not to exceed 80 characters and spaces), author's name (s); institution, and author's mailing address.

c) Articles reporting the results of clinical studies or laboratory investigation should be

organized under the following headings: (1) introduction, (2) material and methods, (3) results, (4) discussion, (5) summary in English and Spanish, (6) references.

d) Case reports will include (1) introduction, (2) description of the case, (3) discussion, (4) summary in English and Spanish, (5) references.

e) Tables, footnotes and legends to figures should appear in separate sheets.

f) If the paper has been presented at a meeting, the place and date should be stated as a footnote.

g) Generic names of drugs should be used. Trade names may also be given in parenthesis, if desired.

h) Metric units of measurement should be used preferentially.

i) Photographs and photomicrographs should be submitted as glossy prints, unmounted. Drawings and graphs should be made in black ink on white paper. All illustrations should be numbered (Arabic) and the top indicated. A legend should be given for each.

j) References should be numbered serially as they appear in the text. The following form will be used:

6. *Koppisch, E.* Pathology of arteriosclerosis. Bol. Asoc. Med. P. Rico 46: 505, 1954. (for journal articles).
4. *Wintrobe, M. M.* Clinical Hematology, 3rd Ed. Lea and Febiger, Philadelphia, 1952, p. 67, (for books).

Abreviations will conform to those used in the Cumulative Index Medicus, published by the American Medical Association.

ADROYD N+
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Relación anabólica-androgénica muy favorable, factor decisivo en la elección de un agente anabólico para el tratamiento de diversos estados clínicos.

El ADROYD (oximetolona, Parke-Davis), ó 17-beta-hidroxi-2-hidroximetilen-17-alfametil-3-androstanona, se expende en tabletas de 5 mg.

INDICACIONES: Estados en los cuales el balance de nitrógeno es negativo: astenia, anorexia rebelde, osteoporosis, fase catabólica de la convalecencia de las intervenciones quirúrgicas, de las enfermedades infecciosas, de las quemaduras severas y de las fracturas, y enfermedades crónicas como la carcinomatosis (excepto el carcinoma de próstata y otros neoplasmas que son estimulados por los andrógenos), la tuberculosis y la artritis reumatoidea.

DOSIS: Administración oral, antes de las comidas o durante ellas, durante 7 a 21 días, hasta un máximo de 90 días. Adultos—de 5 a 10 mg por día o hasta 30 mg cuando estén indicados. Niños—en la estimulación anabólica breve, de 1,25 a 5 mg por día en la primera infancia y de 5 a 10 mg por día en la segunda infancia, durante 7 a 21 días. Como estimulante en la delgadez rebelde o estados de desnutrición puede continuarse el tratamiento durante 90 días en dosis de 1,25 a 2,5 mg en la primera infancia, de 2,5 a 5 mg en la segunda infancia, y de 5 a 10 mg en la adolescencia.

PRECAUCIONES: Debido a que el ADROYD conserva cierta androgenicidad comparte con los andrógenos la tendencia a provocar retención de sal. Debe utilizarse con precaución en las cardiopatías, la nefritis, la nefrosis y las lesiones hepáticas. En los pacientes de edad o cuando se administra por períodos prolongados deben efectuarse estudios periódicos para determinar el estado hepático. Está contraindicado en el carcinoma de próstata y otros neoplasmas estimulados por los andrógenos. Deben vigilarse los lactantes y niños en previsión de cualquier manifestación de masculinización; en caso positivo interrúmpase la administración. En la terapéutica prolongada con ADROYD en los niños debe determinarse la edad ósea cada tres meses, en previsión de cualquier anticipación excesiva de ésta respecto a la edad cronológica, debido al peligro teórico de soldadura prematura de las epífisis.

EFECTOS COLATERALES: Puede ocurrir retención de líquidos lo que generalmente es controlado con diuréticos y otras medicaciones. Puede alterarse la función hepática con dosis elevadas y prolongadas. Las pacientes susceptibles pueden mostrar signos de masculinización, inclusive acné, principio de hirsutismo y alteración del ciclo menstrual. Efectos andrógenicos leves pueden aparecer en los niños.

PR-SJ-3-68

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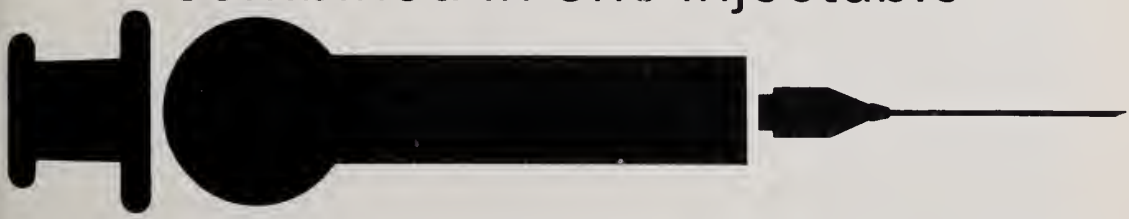
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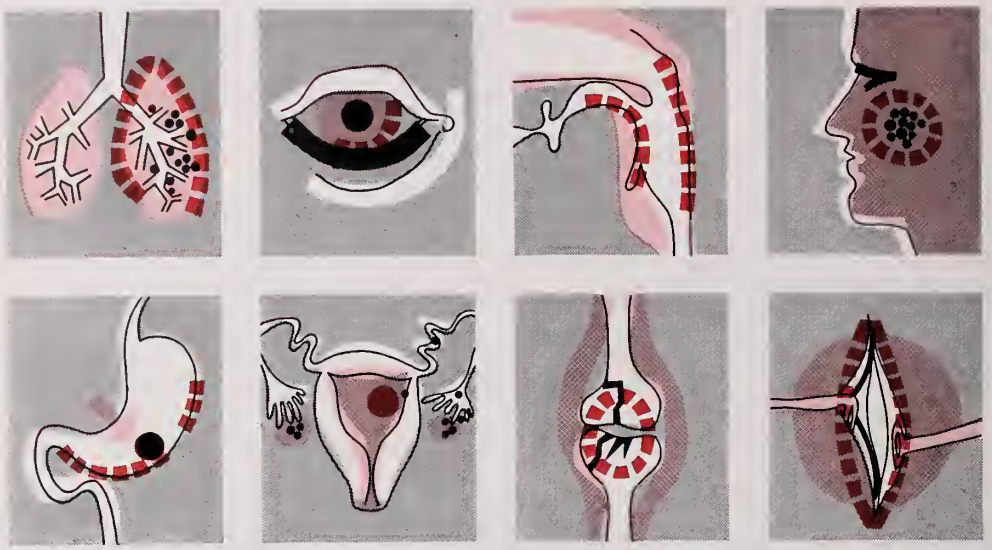
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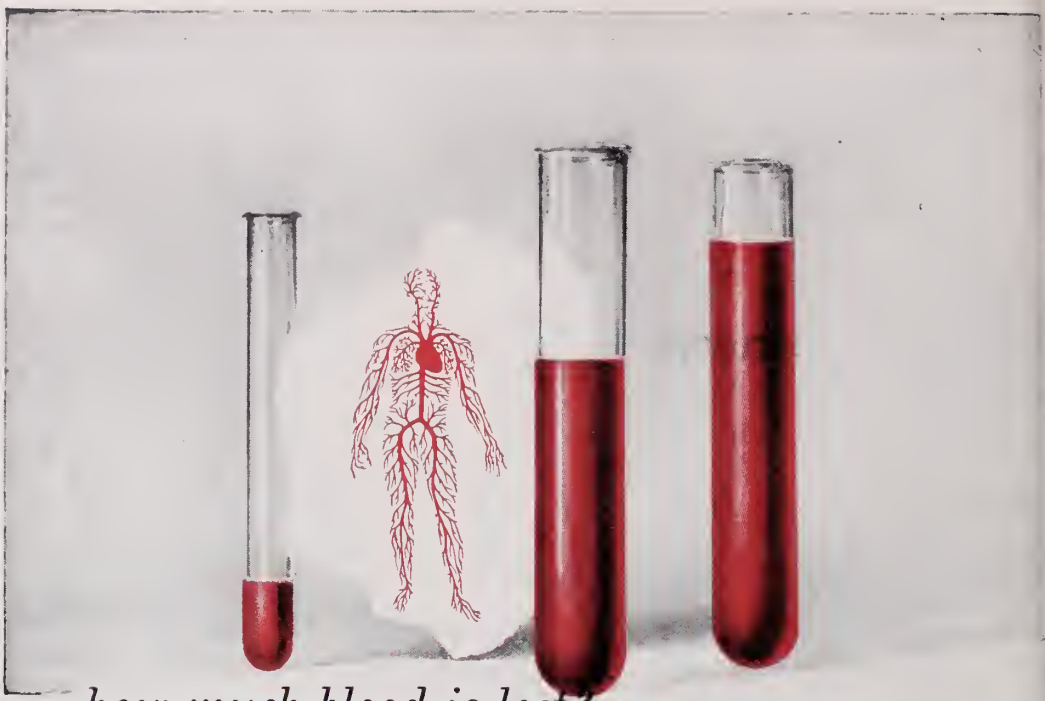
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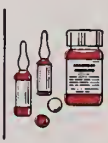
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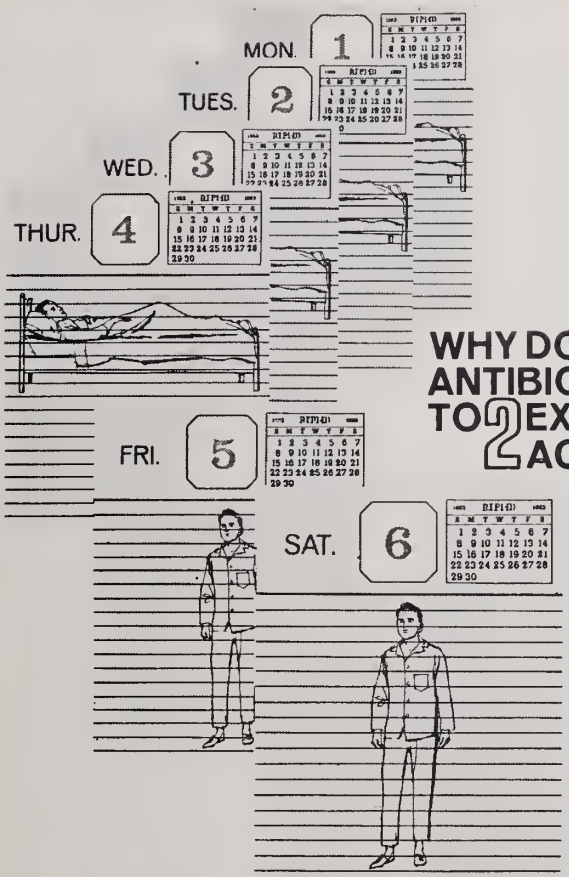
References: 1. Persun, L.: Laryngoscope *74*: 260-266 (Feb.) 1964. 2. Fulton, G.P., *et al.*: Venoms: Am. Assn. Advancement of Science, 1954.

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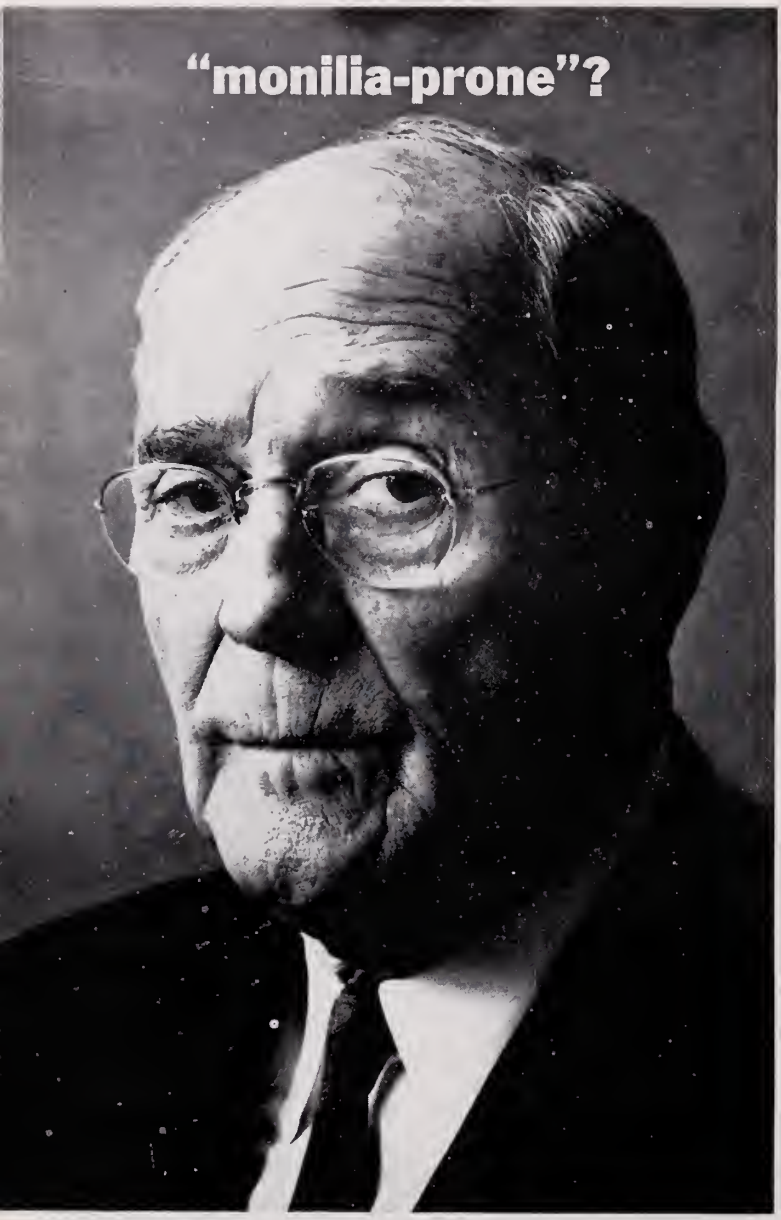
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CANCER DEL SUELO DE LA BOCA

Dr. Antonio Bosch, M.D.
Dr. José N. Correa, M.D.
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En Puerto Rico el carcinoma del suelo de la boca es uno de los tipos más frecuentes de cáncer de la cavidad oral y sigue en incidencia al carcinoma de la lengua. Datos proporcionados por el Registro de Cáncer del Programa de Control de Cáncer del Departamento de Salud de Puerto Rico, nos muestran que durante el período comprendido entre 1950 a 1963 se informaron 894 casos de cáncer de la lengua (base y dos tercios anteriores), 326 casos de cáncer del suelo de la boca y 668 casos correspondían a las demás localizaciones dentro de la cavidad oral (1).

El cáncer del suelo de la boca, aunque se encuentra en una localización accesible, frecuentemente es diagnosticado en etapas avanzadas siendo en ellas mal toleradas las indicaciones terapéuticas tanto quirúrgicas como de radioterapia o combinadas. Este tipo de neoplasia constituye una de las formas más graves encontradas en la cavidad oral y de no ser controlada en sus etapas iniciales, sigue un curso progresivo y fatal.

Presentado en la Sexagésima-Tercera Asamblea Anual de la Asociación Médica de Puerto Rico De la División de Radioterapia y Cáncer del Centro Nuclear de Puerto Rico y el Hospital Oncológico Dr. I. González Martínez

La literatura médica contiene diversas opiniones sobre el tratamiento de elección en cáncer del suelo de la boca. Algunos consideran la cirugía como método único de tratamiento (2, 3, 4), otros autores recomiendan la aplicación de técnicas de radioterapia en todos los casos (5, 6, 7).

Este estudio es un análisis preliminar del problema de cáncer del suelo de la boca en el Hospital Oncológico Dr. I. González Martínez y tiene como objetivo el evaluar los resultados obtenidos con las distintas técnicas de tratamiento.

Material

El material de este estudio comprende los casos con diagnóstico de cáncer del suelo de la boca vistos en el Hospital Oncológico Dr. I. González Martínez.

Durante el período comprendido entre 1940 y 1964 se vieron 145 casos de cáncer del suelo de la boca y todos los casos, excepto 7, tienen confirmación histológica y estos se incluyen en el estudio por haber muerto con evidencia clínica de enfermedad. La T. I muestra la distribución de los casos con relación al sexo y la edad. En nuestra serie, 110 casos (75.3%) se presentaron en hombres y 35 casos (24.7%) en mujeres.

TABLA I: DISTRIBUCION DE LOS CASOS POR EDAD Y SEXO

Décadas	Número de Pacientes		
	Hombres	Mujeres	Total
10-19	0	1	1
20-29	0	0	0
30-39	2	0	2
40-49	19	4	23
50-59	39	5	44
60-69	24	12	36
70-79	23	8	31
80-89	2	3	5
90-99	1	2	3
	110	35	145

La edad promedio del grupo total se encuentra a los 60.6 años, siendo el paciente más joven de 19 años y el más viejo de 90 años.

Factores etiológicos:

Los factores etiológicos que se consideran en los pacientes de esta serie se encuentran agrupados en la T. II. En un gran número de casos, más de un factor se encontraba asociado. La cantidad de tabaco y alcohol consumida por los pacientes no se pudo determinar con precisión y por lo tanto no se hace correlación alguna con estos datos.

TABLA II: FACTORES ETIOLOGICOS

	Tabaco	Alcohol	Higiene Oral Pobre	Leuco plasia	Sífilis
Sí	115	58	83	11	20
No	6	34	12	62	91
Desconocido	24	53	50	72	34

Histopatología:

El diagnóstico de carcinoma epidermoide se hizo en 135 casos. En 7 no se tiene confirmación histológica, 1 caso fue diagnosticado como carcinoma mucoepidemoide, otro como carcinoma epidermoide con componente pseudo-sarcomatoso y un tercero como melanoma maligno.

Extensión de la lesión primaria:

La distribución de los 145 casos de acuerdo a la extensión de la lesión primaria es como sigue: Sesenta (41%) estaban localizados al suelo de la boca sin invasión de estructuras vecinas; treinta y siete de los casos (26%) tenían invasión del borde de la lengua y en 9 casos (6%) la lesión se extendía a la encía y mandíbula; en 31 de los casos (21%) el tumor invadía más de una estructura adyacente o bien se extendía fuera de la cavidad oral (piel o a la orofaringe); en 8 de los casos la información del expediente era insuficiente para clasificar su extensión.

Metástasis linfáticas:

Un total de 92 casos (63.4%) se presentaron inicialmente con evidencia clínica de metástasis a ganglios linfáticos y en el 26% de ellos las metástasis eran bilaterales. En la serie se tiene confirmación histológica de la metástasis ganglionar en solamente 28 casos (30%). Esto se debe al hecho de que antes del 1956 se aceptaba la evidencia clínica como suficiente. Sólo en los últimos años se ha practicado biopsia de aguja para confirmación.

Distribución por estadío:

La T. III nos muestra la distribución de los casos en relación al estadío de la enfermedad. Se

TABLA III: DISTRIBUCION POR ESTADIO DE LA ENFERMEDAD

Estadio	Núm. de Casos
I	34
II	28
III	47
IV	6
Sin clasificar	6
Total	145

consideran dentro del estadío I, todas aquellas lesiones de 2 centímetros o menos localizadas al suelo de la boca y sin metástasis ganglionares. En el estadío II, consideramos aquellas lesiones que miden más de 2 cm. y menos de 4 cm. con metastasis unilaterales operables. En el estadío III se incluyen aquellos tumores mayores de 4 cm. y lesiones con metástasis cervicales unilaterales o bilaterales no operables. En el estadío IV se consideran las lesiones de suelo de la boca que se extienden a la orofaringe o se fijan a la piel y aquellos casos que presentan destrucción franca de la mandíbula.

Tratamiento:

La T. IV muestra la distribución de los casos en relación al tipo de tratamiento empleado.

TABLA IV: TIPO DE TRATAMIENTO

Tratamiento	Número
Radioterapia convencional	32
Cobaltoterapia	32
Implante intersticial *	4
Irradiación externa más implante **	38
Cirugía	14
Irradiacción preoperatoria y cirugía	2
Cirugía más irradiación postoperatoria	2
Electrocoagulación más irradiación	2
No tratados o tratados en otras instituciones	19
Total	145

* Un caso con implante de Ir 192

** Cuatro casos con implante de Ir 192

Diez y nueve de los casos no fueron tratados en nuestra institución, pero algunos de ellos habían recibido tratamiento antes de ser referidos.

Catorce casos (10%) fueron tratados únicamente con cirugía y el resto de los casos tratados en nuestra institución recibió algún tipo de irradiación.

Sesenta y cuatro casos (44%) fueron tratados con radioterapia externa únicamente (convencional 250 Kvp o cobaltoterapia). En 38 casos (36%) el tratamiento con radiación consistió en una combinación de técnicas de radioterapia externa más implante intersticial con agujas de radium o Co^{60}, y en cuatro casos se emplearon semillas de Ir^{192} radiactivo en cintas de Nylon. En 4 casos se usó la técnica de implante intersticial como único método de tratamiento y uno de ellos fue con semillas de Ir 192.

Resultados

Del grupo total, 100 casos pueden ser evaluados para supervivencia de 5 años, de

TABLA V: SUPERVIVENCIA DE CINCO AÑOS EN RELACION CON ESTADIO

Estadío	Número Elegible	Supervivencia Núm.	Supervivencia %
I	27	15	56
II	20	3	15
III	35	5	14
IV	12	1	8
No Clasificados	6	0	0
Total	100	24	24

TABLA VI: SUPERVIVENCIA DE CINCO AÑOS EN RELACION CON EL TIPO DE TRATAMIENTO

Tipo de	Número	Sobrevida Porciento Supervivencia Núm.	%
Roentgenterapia	32	7	22
Co^{60} teleterapia	7	0	0
Implante intersticial	3	2	(67)
Roentgen o Co^{60} + intersticial	25	10	40
Cirugía	14	1	7
Cirugía + radioterapia posoperatoria	2	1	(50)
Electrocoagulación + radioterapia	2	1	(50)
No tratados en nuestra institución	15	2	13
Total	100	24	24

los cuales 24 casos (24%) están vivos y sin evidencia de enfermedad por un período de 5 años o más. La T. V nos muestra la supervivencia de 5 años en relación al estadío de la enfermedad. Podemos observar que en etapas tempranas (estadio I), la supervivencia de 5 años es del 56%; sin embargo, la curabilidad es baja en los estadíos más avanzados.

La T. VI presenta la supervivencia de 5 años en relación al tipo de tratamiento. Treinta y dos casos fueron sometidos a roentgenterapia convencional y 7 de ellos (22%) sobreviven por más de 5 años. De los 7 casos tratados exclusivamente con cobaltoterapia, ninguno vive a los cinco años; y es importante mencionar que 5 de los 7 casos se encontraban en etapas avanzadas de la enfermedad.

De los 14 casos tratados con cirugía, solamente uno, clasificado como estadío I, vive más de 5 años; 6 de los casos tratados con cirugía se encontraban en estadíos I y II y 8 en el estadio III.

Ninguno de los casos en nuestra serie tenía metástasis a distancia, cuando se hizo el diagnóstico inicial.

Del grupo total, 20 pacientes (13.8%) desarrollaron un segundo primario y 4 de ellos presentaron más de dos lesiones primarias.

Discusión

En la literatura se cita al cáncer del suelo de la boca como un tipo de cáncer poco frecuente en la cavidad oral (2, 6, 8, 10), pero en nuestro medio sigue en frecuencia al carcinoma de la lengua y es uno de los tumores más agresivos de la cavidad oral.

Se menciona en la literatura que la incidencia del carcinoma del suelo de la boca en la mujer es muy raro (8, 10, 11); en nuestra serie el 24.7% de los casos se presentó en mujeres y el más joven de los casos se presentó en una mujer de 19 años.

Entre los factores etiológicos asociados a este tipo de neoplasia se han mencionado el alcohol, tabaco, higiene oral pobre y sífilis (8, 9, 10, 11). En nuestra serie se encontraban asociados más de uno de estos factores en la mayoría de los casos y en 20 de ellos la serología era positiva.

En esta serie el tratamiento de elección fue con técnicas de irradiación y el resultado en lesiones tempranas es de un 56% en estadíos I. El implante intersticial en lesiones tempranas, limitadas únicamente al suelo de la boca y sin metástasis ganglionares, puede considerarse como uno de los métodos de tratamiento de mayor valor.

La complicación más frecuente cuando se usan técnicas de irradiación es la osteonecrosis. En nuestra serie se presentó en 10 de los casos tratados. Esta complicación puede evitarse con la extracción pretratamiento de los dientes que se encuentran en el área de irradiación y aquellos que se encuentran en mal estado y evitando las infecciones de la región irradiada.

Se prefiere la cirugía como tratamiento de elección en aquellos casos donde existe invasión de la mandíbula por tumor; pero no debe de considerarse la invasión ósea como contraindicación absoluta para radioterapia.

Técnicas combinadas de radioterapia y cirugía pueden emplearse con éxito en lesiones extensas principalmente en aquellas que no invaden la línea media.

Resumen

Se revisa la experiencia del Hospital Oncológico Dr. I. González Martínez en 145 casos de cáncer del suelo de la boca tratados entre 1939 y 1964.

La supervivencia de 5 años es de 24% para el grupo total, pero debe de tenerse en cuenta que 63.4% de los casos en nuestra serie tenían metástasis ganglionares. En estadío 1 la supervivencia es de 56%.

La radioterapia debe de considerarse como uno de los métodos de elección en lesiones tempranas.

Summary

The experience with cancer of the floor of the mouth treated between 1939 and 1964 at the Dr. I. Gonzalez Martinez Oncologic Hospital is reviewed.

The five years survival for the entire group was 24%, in spite of the fact that cervical lymph node metastases were present in 63.4%. The 5 years survival of stage I cases was 56%.

Radiotherapy should be the treatment of choice in early lesions.

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DISSECTING ANEURYSM OF THE AORTA

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The leakage of circulating blood into the wall of its vessel has been called dissecting aneurysm. It is not a true aneurysm and in reality is a hematoma, but comman usage has made the term acceptable to the medical profession.

The most dramatic and alarming clinical picture occurs when the dissection is in the aortic wall. Dissecting aneurysm of the aorta has a large mortality and was not diagnosed clinically in most series pubished (1).

With the advent of modern cardiovascular surgery the mortality rate of this condition has been significantly, lowered, making its diagnoses a practical necessity. (2, 3, 4).

A dissecting hematoma into the wall of the aorta may occlude many of the great vessels arising from it. The blood supply to the brain, heart, intestinal tract or kidneys may be affected giving rise to confusing clinical pictures. The picture of acute pancreatitis, renal infarct, acute myocardial infarction or a cerebral vascular accident may be mimicked by this condition.

At the present the condition is diagnosed more often than in the past, but it is still diagnosed in only a small percentage of the cases prior to post-mortem examination. Willius and Gragg (5) state that the reasons for the failure on diagnoses are: the relative infrequency of the condition, the absence of a characteristic syndrome, the limitations of special diagnostic adjuncts and the universal lack of clinical suspicion. The latter reason has been thought to be the most important one.

The actual incidence of this condition is difficult to determine. In many cases death is instantaneous and the patient never reaches a hospital. Mote and Carr (6) stated that 1.1% of all cases of sudden death were due to dissecting aneurysm. The authors were coroners of the city of San Francisco and claimed that probably their figures are higher than those reported in hospitals because they deal with a group of sudden deaths which made hospitalization impossible. Glendy and associates (7), in 1937, found 19 cases in 8,200 autopsied at the Massachusetts General Hospital over a 38 year period, an incidence of one in every 431 autopsies. Gouley (8), en 1940, found in Philadelphia that dissecting aneurysm of the aorta occurred in one of every 480 autopsies. The incidence in our University (District) Hospital is that of 8 cases in 2716 consecutive autopsies from 1962 to 1965.

We will describe the clinical picture of these 8 cases (see Table I) and attempt to emphasize in 5 cases some features that should enable one to make an early diagnosis.

From the Department of Medicine University of Puerto Rico School of Medicine, San Juan, P.

Case Reports

Case 2: A 68 year old colored male was admitted on November 28, 1963 with history of a sudden, severe stabbing pain in the precordial region which radiated to the lefh shoulder and along the medial aspect of the left arm and accompanied by numbness and paresthesia of the arm, dizziness and cold sweats. The patient vomited food once. The pain after this episode of vomiting radiated to the left upper quadrant, and was localized at the left flank on admission. Later on it shifted to the xyphoid area. The admitting diagnosis was acute myocardial infarction. Electrocardiogram on admission showed normal sinus rhythm with a rate of 60 per minute, a PR interval of .16 sec. and a mean frontal electrical axis of $+30^{o}$ with changes compatible with an old anteroseptal myocardial infarction and left ventricular hypertrophy.

The patient was a well developed, well nourished, colored male in acute distress. Blood pressure was 100/60 mm. Hg.; pulse, 60/min.; respiration, 20/min. The head and neck were normal. There was an increase in the AP diameter of the chest. The lungs were clear to auscultation and percussion. The PMI was not seen and there was no cardiomegaly to percussion. The heart sounds were distant and no murmurs were heard. The rest of the physical examination was within normal limits except for hypoactive deep tendon reflexes.

Laboratory work revealed a hemoglobin of 10.5; WBC 8,600; hematocrit, 36%. Urinalysis was within normal limits. SGOT was 19 units; SGPT, 5 units and LAD, 280 units on Novenber 28. On November 29, 1963 SGOT was 30 units; SGPT, 5 units and LAD, 495 units. X Ray Chest on admission showed that the heart was enlarged in its transverse diameter with left ventricular preponderance. The aorta was elongated and tortuous with widening f the superior mediastinum. (Fig. 1)

Thirteen hours after admission the patient developed acute precordial pain and cardiac auscultation revealed a grade II systolic murmur and a grade III diastolic murmur best heard in the aortic area radiating to the whole precordium. The clinical impression was acquired aortic insufficiency secondary to dissecting aortic aneurysm.



Fig. 1. *Case* 2: X Ray Chest P A view on November 28, 1965 showing bordeline cardiomegaly with left ventricular configuration. The aorta is prominent in both ascending and descending portions with calcification in its knob. There is also prominence of the brachicephalic vessels. The lungs were clear. On the basis of this film serial studies were ordered to rule out dissecting aneurysm of the aorta.

Electrocardiogram taken after the onset of precordial pain showed a sinus bradycardia of 44/min. and a 1º AV Block with left ventricular hypertrophy and changes compatible with anteroseptal myocardial infarction. (Fig. 2)

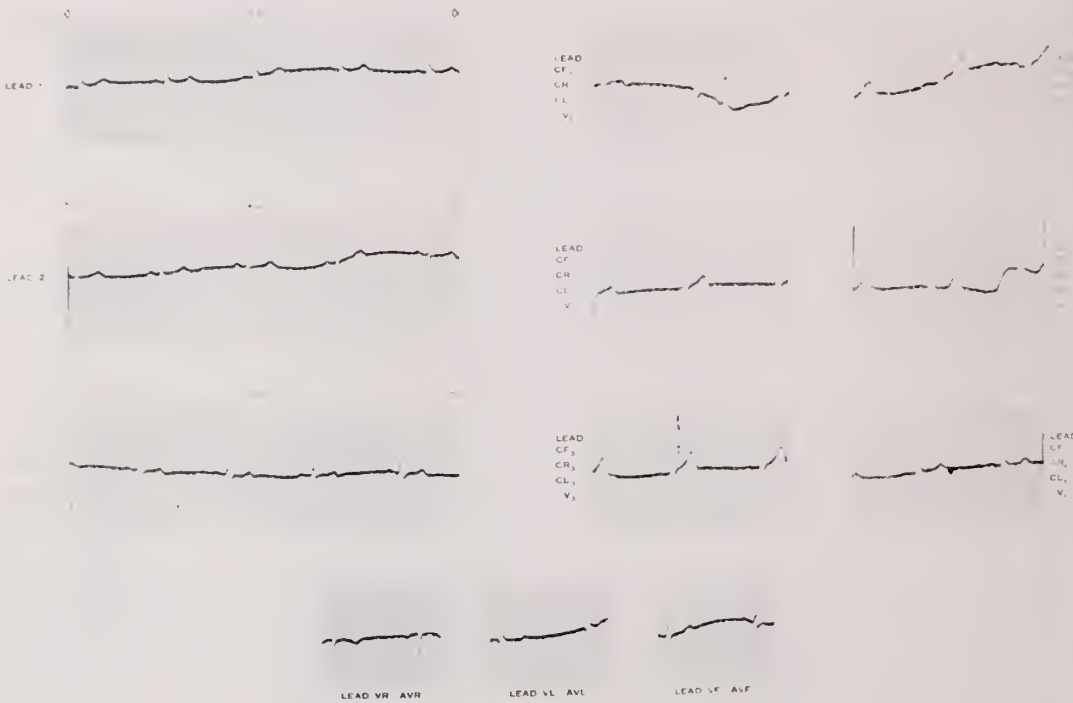


Fig. 2, *Case* 2: Electrocardiogram taken 13 hours after admission (November 28, 1963) shows sinus bradycardia with a rate of 44 beats per minutes: a PR interval of .24 seconds compatible with 1° AV block with an old anteroseptal myocardial infarction and left ventricular hypertrophy by voltage.

Vectorcardiogram failed to show myocardial infarction. X-ray of the chest on November 29, 1963 showed "a fusiform aneurysmal dilatation of the ascending and descending aorta with considerable enlargement of the left ventricle and clear lung fields" (Fig. 3) The patient was seen by a surgical consultant who recommended an aortogram to corroborate the possible diagnosis of dissecting aneurysm of aorta. An aortogram was performed confirming the diagnosis. (Fig. 4) November 30, 1963 the patient became noisy and restless and minutes later was found dead in bed.

Autopsy showed a dissecting aneurysm of the aorta that extended up to the right carotid artery at the level of the middle portion of neck and down to the left iliac artery at the level of the inguinal canal. The ascending aorta showed a bluish black hematoma. At the level of the base of the aorta, to the left there was a rupture about 1 mm in diameter. The left renal artery was also involved by the dissection. Microscopically the aorta showed marked atherosclerosis and medial cystic changes consistent with Erdheim's medionecrosis (showing metachromatic material with toluidene stain).







Fig. 3, Case 2: X Ray Chest P A view and both obliques on November 29, 1963; at this particular time there have been definite widening of the mediastinal shadow at the waist and supracardiac portion. The lungs were again clear. On the basis of these findings the diagnosis of dissecting aneurysm of the aorta was made.

Comments:

This is a case of dissecting aneurysm which simulated clinically an acute myocardial infarction on admission but the sudden appearance of an aortic diastolic murmur plus the X-ray appearance of the aorta made us suspect the presence of a dissecting aneurysm of the aorta. Unfortunately the patient died prior to any surgical attempt.

Case 3: A 50 year old white male was admitted on March 6, 1965 to the University Hospital with history of a sudden crushing chest pain which made him collapse to the floor 2 hours prior to admission. On arrival to the Emergency Room he was found in shock and norepinephrine 4 mg in 1000 ml 5% glucose I.V. was started. After therapy



Fig. 4, *Case* 2: Intravenous aortogram performed on the afternoon of November 29, 1963 confirmed the impression of disecting aneurysm of the aorto extending from the ascending portion to mid-descending portion of the aorta.

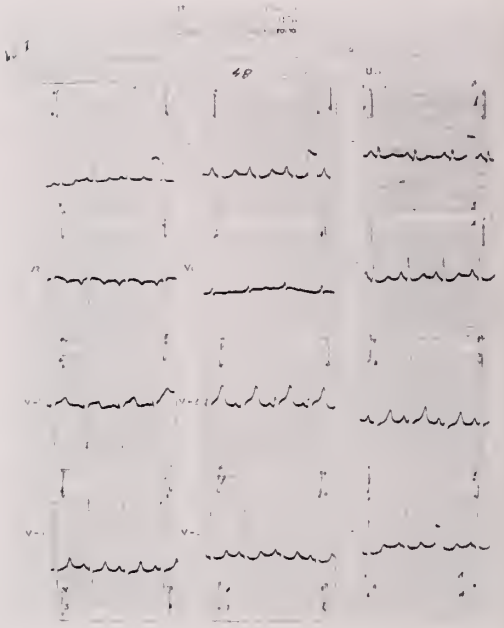


Fig. 5, *Case* 3: Electrocardiogram taken on admission on March 6, 1965 showing normal sinus rhythm with a rate of 91 contractions per minute; a P R interval of .16 seconds, and an electrical axis of + 45º with changes compatible with left ventricular hypertrophy and old diaphragmatic myocardial infarction with tall peaker T waves in V_2-V_3 and peaker P in L_2 and V_3-V_5.

his blood pressure went up to 100/70 and the pulse was 100/min. and regular. An electrocardiogram taken at the Emergency Room showed a normal sinus rhythm with a rate 91/minute and changes compatible with left ventricular hypertrophy and an old diaphragmatic myocardial infarction with tall peaked T waves in V_2-V_3 and peaked P in L_2 and V_3-V_5 (Fig. 5).

Physical examination showed a well developed, well nourished white male looking pale, cold, clammy and disoriented with distented neck veins in the supine position, with good carotid and faint radial pulses. The remaining peripheral pulses were normal. The heart was enlarged to percussion and the heart sounds were distant with a diatolic gallop. Two diagnoses were considered on admission; acute myocardial infarction and pulmonary embolism. At 1:50 PM he was found cold, clammy and the blood pressure was not obtainable. He did not respond to norepinephrine and developed signs of pulmonary edema.

Electrocardiogram showed a complete AV block with idioventricular rhythm (Fig. 6) and later on changed to ventricular fibrillation and cardiac arrest. He did not respond to any measure and was pronounced dead at 2:25 PM.

Autopsy showed a dissecting aneurysm of the aorta extending to the origin of the coronary arteries and distally it reached the aortic valves. A longitudinal tear measuring 3.5 cm in length was located on the posterior intima at 1.5 cm from the

posterior cusp of the aortic valve. Microscopically the aorta showed altherosclerosis, vascularization of the mesoaorta, endarteritis of the advential vessels and thickening and vascularization of the adventitia.

The left kidney capsule striped off with marked difficulty. The external surface was scarred and finely granular and showing small well circunscribed rubbery nodules. The corticomedullary marking were poorly outlined. The ostium of the renal artery was filliform due to an atherosclerotic plaque. Microscopically the left kidney showed cortical adenomata, chronic pyelonephritis and atrophy with arteriolar nephrosclerosis in the right kidney.

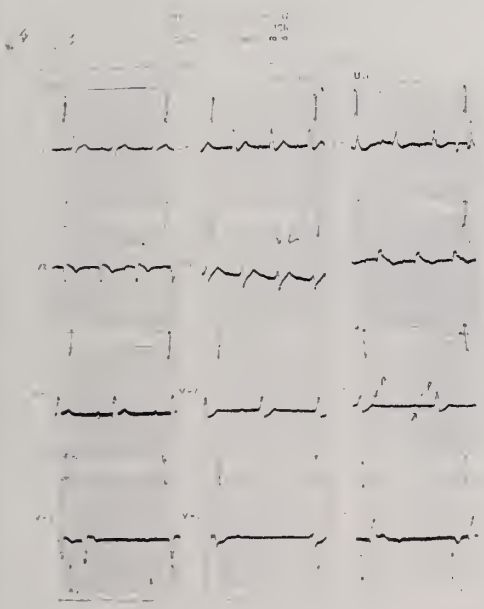


Fig. 6, *Case* 3: This electrocardiogram was taken half hour after the first one. (March 6, 1965); patient was in shock with signs of pulmonary edema. It shows complete A V block with idioventricular rhythm (note the abnormal impulse spread through the ventricle, specially in the precordial leads (V_3) as compared with the ventricular impulse spread on the electrocardiogram at admision). Usually with this slow rate there is a greater likelihood of ventricular standstill with a high incidence of Stokes-Adams attacks.

Comments:

This case shows the presence of complete A-V block secondary to a dissecting aneurysm of the aorta. Our clinical diagnosis was acute myocardial infarction. This type of cases should be treated with pacemakers until the cardiac rate is stabilized and if the patient survives, and the presence of a dissecting aneurysm of the aorta is corroborated, surgical treatment for its correction is indicated.

Case 4: A 62 year old white female hypertensive for the past 6 years was admitted on April 6, 1964 with history of nausea, vomiting and pain in the right upper quadrant of three days duration. The patient was seen at the local Health Center where she was found hypotensive and was rushed to the University Hospital with the diagnosis of acute cholecystitis with shock and possible acute hemorrhagic pancreatitis.

On admission the blood pressure was 100/70 mm Hg and it was the impression of those who admitted her, that she had an acute cholecystitis. Her pulse was 92/min. The patient was a well developed, dehydrated, acutely ill white female.

The lungs were clear to auscultation and percussion. She had normal peripheral pulses. The heart was within normal limits. The abdomen was soft with tenderness and rebound tenderness in the right upper quadrant. There was a questionable mass in the right upper quadrant. The remaining of physical examination was within normal limits. The hemoglobin was 8.5 g; WBC 9,300, hematocrit 35%, BUN, 58 mg%; urinary sediment showed many WBC, 3-6 RBC and many hyaline granules casts, urine albumin was 2.

The electrocardiogram showed sinus rhythm with first degree AV block. The rate was 89/min. Diffuse ST-T changes compatible with diffuse

myocardial disease orpericarditis were present (Fig. 8). The venous pressure was 150 mm of water.

The patient was dehydrated and with a poor urinary output. In spite of hydration measures she remained anuric and was found dead in bed on April 7, 1964.

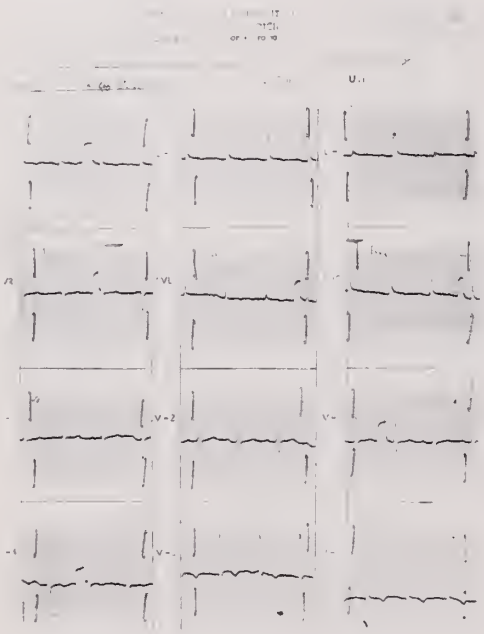


Fig. 7, *Case* 4: The electrocardiogram on April 6, 1964 shows normal sinus rhythm with first degree A V block (PR interval of .22 seconds); an exis of + 45º with diffuse ST-T changes compatible with diffuse myocardial disease or pericarditis.

Autopsy showed a large dissecting aneurysm of the aorta which extended from the arch of the aorta down to the iliac arteries with a large tear 2 cm above the aortic valves. The mediastinum showed a large interstitial hemorrhage with a distended pericardial sac containing approximately 800 ml of blood. The lungs showed acute edema. The patient died from the cardiac tamponade caused by the ruptured dissecting aneurysm.

Comments:

Our admission diagnosis on this patient was acute hemorrhagic pancreatitis. This case is another example of the cases of dissecting aneurysm who present themselves as acute abdominal catastrophes. Since pancreatitis is reported to produce T wave changes in the electrocardiogram we had no clue to make the diagnosis. The lesson in this case is that one should examine carefully patients who are hypertensives and present themselves with acute abdominal pain. The sudden appearance of diastolic murmurs at the aortic area, the



Fig. 8, *Case* 6: X Ray Chest PA view on November 30, 1964 showing borderline cardiomegaly with prominent ascending and descending limbs of the aorta. There is some suggestion of calcification in the descending limb of the aorta. The lungs are clear.

changes in the peripheral pulses, the widening of the aortic outline and the presence of urinary findings should be carefully looked for. In suggestive cases an aortogram may be diagnostic.

Case 6: A 60 year old colored male was well until 20 years before admission when he developed shortness of breath. He was seen by a physician for those symptoms who told him he was hypertensive. He took some pills for three months and was relieved.

Six years later he was told to have diabetes mellitus and was treated with tolbutamide. His diabetes was controlled with this drug.

Four months prior to admission he developed suprapubic discomfort, slight dysuria, frequency and nocturia. He was told by his family physician to have an urinary infection and was treated with yellow pills without improvement. Two months prior to admission, he was seen for the first time at the University Hospital Emergency Room with a history of dizzy spells, headaches, suprapubic discomfort, urgency, frequency, right costovertebral angle tendernes, 4 albuminuria and a blood pressure of 160/100 mm Hg. The clinical diagnosis was an urinary infection and was sent home on a sulfonamide. Six day prior to admission while driving a car he developed sudden, dull, severe left flank pain radiating to the lumbosacral region and to the anterior chest. This was accompanied by slight dyspnea on exertion.

The flank pain persisted almost constantly although less severe and he was seen in our Emergency Room on November 18, 1964 and admitted to the hospital. The initial impression was renal disease with hypertension.

The physical examination showed a blood pressure of 250/140 mm Hg in the left upper extremity and a pulse of 86/minutes. The patient was a well developed, well nourished slender mulatto male in moderately acute distress. The ocular fundi could not be visualized. The chest was clear to auscultation and percussion. The PMI was at the 6th intercostal space at the anterior axillary line. The aortic second sound was accentuated. A grade II systolic soft murmur and a grade II diastolic murmur were heard at aortic area. The peripheral pulses were normal bilaterally and there was a marked left and minimal right costovertebral angle tenderness. The hemoglobin was 11.2 g%; hematocrit, 35% and WBC 15,150. Urinalysis revealed a 3+ albumin, 0-2 WBC/HPF, 2-3 RBC and 4-6 granular casts. FBS was 111 mg%. The two hours post-prandial blood sugar was 171 mg.%.

The BUN fluctuated from 43.8 mg% on admission to 55.0 mg% on November 24, 1964. The VDRL was negative; creatinine 3.85 mg; SGOT, 22 units; SGPT, 22 units and LAD, 540 units. The X-ray of the chest showed cardiac enlargement with left ventricular hypertrophy and clear lung fields (Fig. 8). The ECG on admission showed normal sinus rhythm with a rate of 90/min. and an mean electrical QRS axis of $+70^{o}$ with left ventricular hypertrophy and non specific T waves changes (Fig. 9). A renogram was abnormal bilaterally with poor vascular segments in both and an abnormal excretory phase bilaterally. An intravenous pyelogram showed poor visualization of the renal structures.

The patient was placed at bed rest, sedation and antihypertensive drugs (reserpine .5 mg. daily) on admission. The blood pressure dropped to 180/120 mm. Hg. Later on hydralazine was added. The diagnosis was bilateral renal parenchymatous disease, probably pyelonephritis and renal hypertension.

During his entire hospitalization the patient complained of dull left flank pain. On November 30 a diastolic gallop was heard and in that evening a pericardial friction rub was heard at 4th left intercostal space near the sternal border. The lungs were clear. This was thought to be incipient congestive heart failure accompanying uremic pericarditis and digitalization was started. On November 30, 1964 at 2:00 PM the patient became disoriented. The blood pressure was 190/130 mm Hg and the pulse of 84/min. On December 1, 1964 he improved but at 7:30 AM of the next day he had a cardiac standstill and external cardiac massage failed to start the heart beat. He was pronounced dead at 7:30 AM of December 1, 1964.

TABLE I: FINDINGS IN EIGHT CASES OF DISSECTING ANEURYSM OF THE AORTA

	Age (Yr.)	Sex	Race	BP (mm Hg)	BUN (mg %)	Enzymes	Urines	CBC	Peripheral Pulses	Pain	Cardiac Findings	X Ray Chest	ECG
Case 1	75	M	W	90/60	43.2	———	3-7 WBC; Albumin -3/-	Hg. 82% 11.9 gms; Ht.- 38%	Normal	Severe Substernal pain without radiation	Normal	———	———
Case 2	68	M	C	100/60		SGOT 30 SGPT 5 LAD 495	Occasional WBC; Few Bacteria; Few Ephitelial cells	Hg: 81.4%; 11.8 gm; Ht.: 36%; WBC:7,800	Active	Severe precordial pain radiating to left arm and left upper quadrant	Cardiomegaly grade; II systolic and grade III diastolic murmur radiating to neck	Enlargement of heart in its transverse diameter with left ventricle preponderance. The aorta is elongated and tortuous. Aortogram showed fusiform aneurysm of ascending and descending aorta. Clear lungs.	Left ventricular hypertrophy; old auteroseptal myocardial infarction
Case 3	50	M	W	90/70 to %	———	———	———	———	Faint Radial pulses; good femoral pulses	Crushing retrosternal pain of recent onset	Cardiomegaly to percussion; distant sounds; diastolic gallop; no murmurs	———	Left ventricular hyperttrophy; old diaphragmatic myocardial infarction to complete AV Block
Case 4	62	F	W	140/110	58	Serum Amylase 82 to 130 units	Loaded with WBC., 3-6 RBC; many Hyaline granular casts; Albumin 2/-	Hg 8.5 gms. 58.6% Hematocrit 31% WBC. 9,300	Good	Severe right upper quadrant pain with right CVA tenderness	No cardiomegaly; Distant heart sounds, no murmurs	———	I° AV Block; Suggestive of LVH
Case 5	63	M	W	160/100	42	———		———	Normal	Severe Stabbing Epigastric pain	No cardiomegaly No murmurs No thrills Distant sounds	———	I° AV Block; Suggestive of LVH

TABLE I: CASES OF DISSECTING ANEURYSM OF THE AORTA (CONCLUSION)

	Age (Years)	Sex	Race	BP (mm Hg)	BUN (mg. %)	Enzymes	Urines	CBC	Peripheral Pulses	Pain	Cardiac Findings	X Ray Chest	EKG
Case 6	60	M	C	250/140	43.8 to 51.0	———	0-2 WBC; 0-2 RBC Albumin 3/- 4-6 granular casts	Hg. 10 gms. Hemat. 27 WBC 10,000	Normal	Severe left flank pain radiating to left hemithorax region and anterior chest	Cardiomegaly; Aortic 2nd. Sound accentuated; grade II systolic soft murmur radiating to LSB and grade II diastolic murmur in same region	Cardiac Enlargement with left ventricular hypertrophy with clear lungs	Left Ventricular Hypertrophy by voltage; non-specific T waves changes
Case 7	56	M	W	%	9.4	———	4-5 WBC Few hyaline casts alb. 1 /-	Hg. 81.46 11.8 gms. Hemat. 39% WBC 10,680	Normal	Severe crushing retrosternal pain	No cardiomegaly; grade IIIharsh early systolic murmur in aortic area radiating to apex grade III harsh early systolic base diastolic gallop in apex, distant heart sounds	Marked Enlargement of left ventricle with double contour of the left ventricular segment. Aorta is elongated. The lungs were clear	Changes compatible with anterolateral myocardial infarction
Case 8	62	M	C	170/120 to %	68	SGOT 42 units 42 units LAD 460 units	———	Hg. 78.7% Hemat. 39%	Normal	Severe gripping chest pain	Cardiomegaly; soft blowing systolic murmur in apex and grade II diastolic murmur in aortic focus	Marked Enlargement of left ventricle with opacities in right lower base	Sinus tachycardia a premature ventricular contraction recorded in AVR showed an abnormal q suggestive of myocardial infarction. The rest of EKG showed 1st. degree left bundle ventricular hypertrophy.

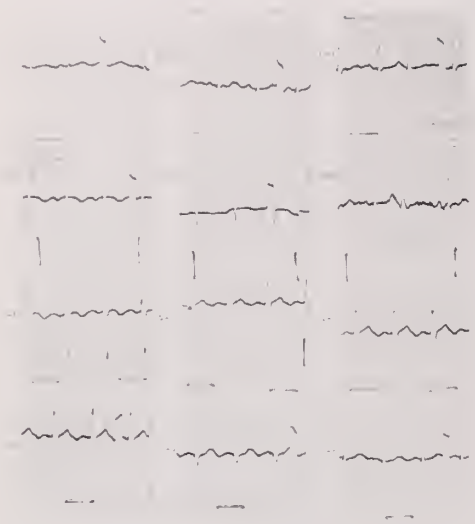


Fig. 9, Case 6: Electrocardiogram on admission (November 18, 1964) showing normal sinus rhythm with a rate of 90 beats per minute with left ventricular hypertrophy and non-specific T wave changes.

The autopsy showed a dissecting aneurysm of aorta with a tear above the right posterior cusp measuring 1.5 cm surrounding the aorta and dissecting into the perivascular tissue and around the pulmonary artery. The aneurysm went up to the entrance of the carotids and subclavians arteries without including them and descending down the left side of the thoracic aorta. There was a marked dilatation of the aorta at the level of the renal arteries. The lumina of the renal arteries were patent. The aneurysm dissected down to about 2 cm above the iliac arteries where a re-entry occurred. There was also an anomalous bifurcation of the renal arteries with an old thrombosis of the branch of the renal artery supplying the anterior pole of the right kidney. No renal infarcts were found. The kidneys showed a chronic pyelonephritis and advancel vascular changes compatible with malignant hypertension or Kimmelstiel-Wilson's syndrome. The cause of death was considered to be acute heart failure secondary to dissecting aneurysm.

Comments:

This was a case of chronic pyelonephritis and renal hypertension who had a dissection of his aorta as a final event on his clinical picture. It is very doubtful that this patient would have recovered even with surgical treatment from his dissection but a case with less severe involvement of his kidney's may have benefited from surgery if the diagnosis had been made earlier.

Case 7: A 56 year old white male on November 8, 1964 while talking with some friends developed a severe non-radiating retrosternal pain accompanied by dizziness. He was brought to the Emergency Room of the University Hospital were he was found cold, clammy and without obtainable blood pressure. The patient denied any history of hypertension. The admission diagnosis was acute myocardial infarction versus dissecting aneurysm of the aorta.

The physical examination on admission revealed a blood pressure 0/0 and a pulse of 64/min. The patient was a well developed, well nourished obese white male in acute distress complaining of pain in the chest. The lungs were clear to auscultation and percussion. The point of maximum impulse of the heart was not seen and a grade 111 systolic murmur was heard over the precordium. There was cardiomegaly by percussion. The remaining of the physical examination was essentially negative. Upon admission an electrocardiogram showed normal sinus rhythm with a rate of 89/min. with occasional premature atrial and ventricular contractions and changes compatible with an anterolateral myocardial infarction (Fig. 10).

After the shock was treated with metaraminol intravenously and the blood pressure was raised to 100/80 mm Hg a harsh early grade 111 systolic murmur was heard at the aortic area radiating to the apex. A grade 111 diastolic murmur best heard

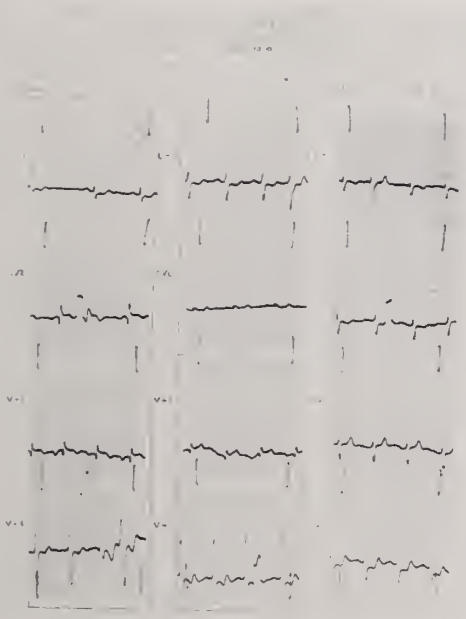


Fig. 10, *Case* 7: Electrocardiogram on admission on November 8, 1964 showing normal sinus rhythm with a rate of 89 per minute with occasional premature atrial and ventricular contractions and changes compatible with an anterolateral myocardial infarction.

at the apex was also noted. There was also an intermittent apical diastolic gallop. The heart sounds were irregular, distant and of poor quality. The hemoglobin was 12.0 g; WBC 10,680; hematocrit, 39%; BUN, 9.4 mg%; FBS 94 mg%. Urinalysis showed albuminuria, 4-5 WBC/HPF and a few hyaline casts. X-ray of the chest showed enlargement of the left ventricle with a double contour of the left ventricular segment suggestive of a left ventricular aneurysm. The aorta was elongated (Fig. 11).

On the evening of November 8, 1964 the patient's blood pressure was unobtainable and intravenous metaraminol 10 mg/100ml was started without avail. The patient went into cardiac arrest at 10:20 PM and was pronounced dead minutes later.



Fig. 11, *Case* 7: X Ray Chest PA view taken on November 8, 1964 showing marked cardiomegaly with left ventricular hypertrophy. The aorta is elongated with a prominent descending limb.

On autopsy there was a dissecting aneurysm of the aorta starting above the coronary ostia following the course of the anterior descending branch of the left coronary artery and continuing down the aorta to 6 cm above its bifurcation, with a rupture into left hemithorax at the level of mid thoracic aorta. There was a subepicardial hemorrhage following the course of the anterior descending coronary artery. The aorta also showed moderate arteriosclerosis. The cause of death was dissecting aneurysm of the aorta due to idiopathic medial necrosis.

Comments:

This is a case of dissecting aneurysm which was diagnosed as an acute myocardial infarction. The patient actually had compression of the anterior descending

branch of the left coronary with myocardial damage. This case developed a diastolic murmur of aortic origin during his clinical course. This finding should have been a clue to consider dissection of the aorta as the diagnosis. Aortography is not an innocuous procedure but should be performed in those cases in which there is a strong possibility that dissection of the aorta is the underlying pathology since only in this fashion can the diagnosis be corroborated and surgical correction may be attempted.

Discussion

Most cases of dissecting aneurysm occur between the ages 40 and 70 years, but no age is exempt. The disease has been reported in an infant of 14 months and in a female of "nearly 100 years" (9). No racial predilection has been observed although Levison et al (10) observed in 1950 a high incidence (25.3%) in Negroes which was attributed to the greater frequency of hypertension in this race. Altitude and climate are believed to have no effect on the incidence of dissecting aneurysm.

Little attention has been given to the significance of occupation in dissecting aneurysm. In 1941 Cherry and Cherry (1) studied the role of exertion in the production of dissection, but as Master et al (12) in their study of the relationship of occupation to coronary occlusion they failed to find evidence of occupational susceptibility. It is apparent that dissecting aneurysm involves the skilled as well as the unskilled, the intellectual as well as the manual laborer, so no occupational susceptibility is suggested.

Almost all authorities agree that the basic defect underlying aortic dissection is medial degeneration of the type termed *medio necrosis aorta idiopathica cystica* by Erdheim (13). Cystic medial necrosis is characterized by focal accumulation of mucoid material, principally in the middle and outer thirds of the media of the ascending portion and the arch of the aorta. The elastic and muscle tissues of the media also show degenerative changes, but whether these changes are primary or secondary to the accumulation of mucoid material is controversial. The cause of cystic medial necrosis is not known but its frequency in many conditions suggests that multiple factors may be involved.

A genetic predisposition to medial necrosis has been suggested by the incidence of aortic dissection in persons with Marfan's syndrome (arachnodactyly), a genetic defect of mesodermal tissue. Some inherited factor is suggested by the greater incidence of the condition in cases of thoracic and spinal deformities such as kyphoscoliosis and coarctation of the aorta.

Some have postulated the possibility of an endocrine factor due to its association with pregnancy. Schnitker and Bayer (14) studied 49 women with dissecting aneurysm of the aorta and found that in 24 it was associated with pregnancy and usually occurred in the third trimester.

The commonest clinical finding associated with medial necrosis and aortic dissection is hypertension but the exact role of it is not well understood. Many authorities have observed that dissecting aneurysm occurred in many patients with malignant hypertension.

Syphilis was considered years ago a predisposing factor in aortic dissection, but actually it is more prone to protect the patient from developing it, since it tends to fuse the layers of the vessel.

Arteriosclerosis is frequently present in the aorta with a dissecting hematoma but it has not been found to be causally related to the dissection in most instances. Rarely, aortic dissection is related to mycotic aneurysms.

Bean et al in 1955 (15) correlated dissecting aortic hematoma and skeletal abnormalities which occur in growing rats fed with sweet pea meals (producing lathyrism) bringing up the idea of a dietary factor

predisposing to dissection of the aorta.

The most common symptom in this disease is pain. The pain is more often described as a sudden, severe, tearing excruciating or ripping pain in the precordium. It may become progressively more severe and usually will respond poorly to massive doses of narcotics. It may radiate to the head, neck, shoulders, back, abdomen or suprapubic area. In some cases the pain, may be felt initially in the epigastric area or the flanks. The characteristic type of the pain and its radiation is very important and may be diagnostic, but frequently it mimics an acute myocardial infarction or acute abdominal catastrophe.

It must be remembered that there are cases in the literature in which no (16) pain was reported during the entire course of the illness. Of course, one must have in mind that many of these patients were admitted in shock, comatose or confused and in these circumstances the history of pain may not have been elicited. The pain may subside spontaneously after the initial dissection but recurrence of pain is an omnimous sign since it usually precedes the onset of external rupture. Other presenting symptoms may be sudden hemiplegia, bizarre neurological defects, unexplained shock or epigastric pain accompanied by melena. The typical pain of dissecting aneurym is precordial in location, tearing or crushing in nature with radiation to the back and down to the lumbar area.

Dyspnea may be present in some cases (17). Ecchymoses involving the skin of the lower abdomen, chest or neck have been described but this is a rare finding (18). This finding is believed to be due to the dissection extending along the superficial branches of the aorta.

Most of our patients looked acutely ill with signs of peripheral vascular collapse. The literature has emphasized that most of these patients remain hypertensive in spite of their other findings of shock but in our series 6 out of 8 patients were hypotensive. There was tachycardia and tachypnea in most of them.

Cardiac auscultation revealed diastolic murmurs in 4 of our patients. This is an important sign of dissecting aneurysm (19). The murmur is apparently due to dilatation or deformity of the aortic ring which results from the dissection. These patients were not seen previously by any phisician so the possibility that the murmurs were present before could not be excluded. A new diastolic murmur may help one to suspect the diagnosis.

Nervous system manifestations were present in about 15% of the cases studied by Shennan (20). Scott and Sancetta (21), in a collected study, found that neurological involvement had occurred in 21% of the cases. The neurological findings may consist of disturbances of consciousness, disorientation or confusion with minor disorders including dizziness, stupor, drowsiness and headaches and more complex neurological disturbances such as ischemic necrosis of peripheral nerves, spinal cord and brain giving signs and symptoms corresponding with such lesions (9). In our series one patient was disoriented on admission and all of them went into coma after external rupture of the aneurysm.

Abdominal pain, tenderness and rebound tenderness may be present. One of our patients had a chief complaint of right upper quadrant pain accompanied by tenderness upon palpation. The admission diagnosis was acute pancreatitis.

Involvement of renal arteries may produce symptoms reminiscent of renal calculus or renal infarcts. Hematuria or anuria may be present; one of our patients whose aorta presumably dissected while in the hospital complained of left flank pain. Involvement of the ocular system is infrequent but cases have been reported of blindness scotomata and Horner's syndrome (22).

The hemoglobin and red blood cell count in these patients may be normal in admission if they are admitted soon after

the dissection but tend to fall if the patient survives. Leukocytosis is usually present. Elevation of the blood urea nitrogen is reported in around 50% of cases (9). Retention of nitrogenous substances in the blood is explained by dissection of one or both renal arteries or as due to pre-renal azotemia resulting from shock, dehydration and congestive heart failure. Microscopic hematuria and albuminuria are also a common findings.

The electrocardiogram, although usually abnormal, is not diagnostic. Left ventricular hypertrophy is a common finding as these patients are usually hypertensive. Changes compatible with a diagnosis of acute myocardial ischemia or myocardial infarction may be present if the dissection involves the ostia of the coronary arteries as was expressed by Oram and Halt in 1950 (23). In our cases the dissection involved the coronary arteries in only one case, yet the electrocardiograms were compatible with old myocardial infarction in 3 cases. Complete AV block or partial AV block may be seen. We had one patient who developed Ist. degree AV block. In some cases the external rupture of the aneurysm is into the pericardial sac.

The radiological finding usually consist of enlargement of the heart combined with a) a widened or tortuous aorta, b) pleural fluid, usually on the left, c) a definite aneurysm or d) a progressive enlargement of the aorta on repeated films (3). Sometimes X-rays are not diagnostic but present secondary to hemathorax (3).

The initial event in the vast majority of cases of dissecting aneurysm, as accepted by many known authors, is an intramural hematoma resulting in an area of medial degeneration (Erdheim-Gsele medionecrosis) (13). In our present work 2 cases had proven medial cystic necrosis of the aorta on microscopic examination. The intimal tear formely believed to be the initial lesion is now considered to be secondary to a rupture of the hematoma into the lumen of the aorta.

The literature has supported this concept, describing cases without intimal tear but there have been instances when an intimal tear may start a dissection specially in cases in which the tear is at the base of an atheromatous plaque (24). In six cases of our small series advanced to moderate atheromatosis was described. Many authors agree that arteriosclerosis is frequently present but it is not clear if it is causally related.

The dissecting aortic hematoma having started in the media may extend completely around the vessel or involve only a portion of its circunference. It can also extend proximally, distally or both, and compress or extend along the branches of the aorta.

The initial tear usually occurs in the proximal ascending aorta, less commonly in the descending aorta and infrequently in the arch and abdominal aorta. In our patients the initial tear occurred six times in the ascending proximal aorta and two times in the descending aorta.

Considerable variations in the anatomic and pathological features of dissecting aneurysm have been found. Various classifications have been proposed. We consider the one recently suggested by De Bakey et al (3) useful. They describe three types of dissection, as follows:

Type I — This pattern is characterized by the fact that the dissecting process along with the intimal tear arises in the ascending aorta and extends distally for a variable distance, but usually throughout the remaining aorta and not infrequently into its major terminal branches. There are varying degrees of extent of circunferential involvement, but it is usually incomplete. Aortic valve insufficiency is frequently present.

Type II — The dissecting process is limited to the ascending aorta. The transverse tear in the intima begins above the aortic valve and terminates just proximal to the origin of the innominate artery. The aneurysm assumes a fusiform appearance with a thin outer layer accompanied by

aortic valve incompetence. This type is usually seen in cases of the Marfan's syndrome.

Type III – This pattern is characterized by the fact that the dissecting process arises in the thoracic aorta usually at or just distal to the origin of the left subclavian artery and extends distally for a varying distance.

In this review there were five type I cases, one type II cases and two type III cases.

Secondary or re-entry tears may occur at any point distal to the initial tear. Reentry produces a second channel in communication with the aortic lumen. Our case number 6 was the only one where re-entry occurred. This was a Type I pattern and reentry occurred 2 cm above the origin of left iliac artery. This new channel may be obliterated by a thrombus or can be endotheliolized forming a double aorta. More common is an external rupture of the hematoma, ending in death. The rupture can occur most frequently into the pericardium, left pleural cavity, right pleural cavity, mediastinum, abdominal cavity or the gastrointestinal tract.

External rupture of the hematoma is the most frequent couse of death. Congestive heart failure is the second most common cause of death.

Summary

Between 1962 and 1965 eight cases of dissecting aneurysm of the aorta were found among 2,716 consecutive autopsies done at the University (District) Hospital. All cases were in people past 40 years of age. Seven were males and only one was a female. Pain in the chest, abdomen, and flanks was the most prominent symptom although most patients became disoriented or comatose a few hours later. A diastolic bruit, bizarre neurological signs, changing peripheral pulses and variable degrees of anemia are of diagnostic value. The protean manifestations of dissecting aneurysm may mimick many clinical entities.

The cases presented demostrate the variation in clinical picture and the lesson learned from each which could alert us to a correct diagnosis.

When the diagnosis of dissecting aneurysm is seriously considered aortography may corroborate it. The risk of aortography is worth taking since surgical treatment of this condition has significantly lowered its mortality.

Resumen

Entre 2,716 autopsias consecutivas ejecutadas en el Hospital (de Distrito) Universitario entre los años de 1962 al 1965 se encontraron 8 casos de aneurisma disecante de la aorta. Todos los casos hallados fueron en personas mayores de 40 años; siete casos del sexo masculino y sólo uno en el sexo femenino. Dolor en el tórax, en el epigastrio, hipogastrio, o en la región lumbar fue el síntoma más prominente aunque en casi todos los pacientes, sobrevino un estado de desorientación o coma unas horas después.

Un soplo diastólico aortico, signos neurológicos poco corrientes, pulsos periféricos cambiantes y grados variables de anemia son de importancia en el diagnóstico. Las manifestaciones complejas de esta entidad pueden enmascararse como muchos cuadros clínicos. Los casos anteriormente expuestos, nos demuestran la variedad con que se presenta y la moraleja aprendida en cada uno de ellos nos hace estar en guardia hacia el diagnóstico certero. Las aortografías confirman este diagnóstico y sus peligros no deben ser sobreestimados ya que se le ofrece al paciente un medio para llegar a un diagnóstico más veraz.

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PUBLIC HEALTH ASPECTS OF THE POST-PARTUM CERVIX

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The early recognition of pre-invasive cancer of the uterine cervix and the complete elimination of the invasive form of this disease has come to rest squarely on the shoulders of those who care for women during the child-bearing period (1). This burden applies equally to the general practitioner as well as the obstetrician. The day in which the physician sees the patient for the first time when she is ready to deliver is fast passing from the scene (2). Likewise, increasing numbers of patients are returning to their physician for routine check-ups in the intermediate post-partum period. Both of these conditions may be utilized to practice preventive medicine of the highest caliber. Several opportunities are thus available to study the cervix and to diagnose and treat abnormal conditions in their earliest stages. Lack of attention to the cervix in the post partum period may lead to tragic consequences. Diligent adherence to this aspect of the care of the patient during the puerperium has doubled the incidence of carcinoma being found during this short period of time (3).

In reality, the best care of the post-partum cervix starts before the baby is born. No patient should go thru pregnancy without a complete examination of the cervix. This is most conveniently done when the patient is first seen regarding the possibility of her being pregnant. It may and should be repeated in the mid-trimester and shortly before term. The idea that the introduction of a speculum into the vaginal canal either is capable of producing or aiding in the process of abortion is absolutely untenable.

The "trauma" involved in such an examination is not nearly that involved in the act of coitus. The speculum examination alone is not enough; a Papanicolau smear must be taken on every patient no matter what her age or parity may be. Biopsies should be done when indicated. The elimination of any part of the total examination of the cervix simply because a patient is pregnant may lead to her untimely and unnecessary demise.

Immediate Post Partum Care

Routine Inspection of the Cervix. Textbooks of obstetrics are not in agreement as to whether or not each and every post-partum cervix need be completely visualized and examined in the absence of breech, forceps or operative delivery. The reason advanced by those who do not favor the procedure is that this extra manipulation is attended by an increased incidence of infection. However, the literature contains articles to the contrary. Many clinicians not only inspect the cervix but

routinely manually explore the uterine cavity. Both of these procedures do not seem to be associated with an increase in morbidity and mortality. Digital intravaginal examination cannot be relied upon to reveal pathologic conditions because the cervix is so flabby (4). It is therefore our contention that the delivery is not complete when the placenta is in the basin and the last stich is in the episiotomy. It is only complete when the cervix has been completely visualized.

Methods of Inspection. There are two methods available to obtain good inspection of the postpartum cervix. In the first, the anterior lip of the cervix is gently grasped with a ring forceps after it has been exposed either manually or with retractors. Gentle traction is then applied, while pressure on the uterine fundus from above brings the whole organ lower down in the pelvis and aids in the procedure. As the anterior cervical lip comes into view outside of the introitus, additional ring forceps are used to "walk around" the cervix and inspect it thoroughly.

If ring forceps are not available, an excellent view of the cervix is afforded by a modification of the Brandt-Andrews maneuver in which the uterine fundus is pushed upward and out of the pelvis by a hand on the abdomen. When this is done in the presence of proper vaginal retraction, the entire cervix may be visualized at a glance at the level of the pelvic brim. (5, 6)

Immediate Repair of Post-Partum Lacerations. No cervix participates in parturition without damage and trauma. This is a basic and inevitable fact. Minute tears are always present following labor and delivery. Generally they heal well by themselves, and only rarely do they give rise to later symptomatology. Deep tears, on the other hand, are far more dangerous. Not only may they be the cause of massive hemorrhage leading to shock and/or death, but other problems may arise in the future. Adequate spontaneous union rarely takes place, and deformity is the result. This holds especially true if the laceration has extended towards the broad ligament. Immediate repair, on the other hand, accomplishes the folowing things: 1) blood loss is diminished, 2) healing is anatomic, 3) cervical incompetency is prevented, 4) infections are minimized and, 5), the need for future surgery is obviated (7).

Biopsy of the Post-Partum Cervix. Because the cervix invariably undergoes laceration during the process of delivery, if is often difficult to say what is normal and what is abnormal from the gross appearance. However, the presence of areas of increased firmness to touch or pedunculated and polypoid masses or lesions which appear to be extending from the cervix out onto the vaginal mucosa should arouse the highest suspicion. All such lesions, in part or in toto, must be biopsied and sent for microscopic examination. The importance of informing the pathologist that the tissue submitted came from a pregnant cervix cannot be stressed too strongly, because there are certain microscopic changes seen in pregnancy which may be confusing in themselves.

One should not be afraid to perform a cervical biopsy even if a punch forceps is not available. The scalpel or the episiotomy scissors will do quite well in a pinch. Any bleeding can be controlled immediately with a figure-of-eight suture using chromic cat-gut. It is advisable to make a small drawing of the lesion in the record where it may be kept for later comparison.

Differential Diagnosis. Not uncommonly coandylomata accuminata are seen on the cervix at the time of parturition. The size of the individual lesion is variable, and they may be present in the vagina and on the external vulvar surface as well. They bleed easily when cut or torn. Partial inversion of the uterine fundus may present with a mass protruding thru the cervical os. Likewise, a submucous fibroid or polyp may prolapse shortly after the delivery of the infant and placenta. In this latter case the stalk leading to the fundus serves to point out the true nature of the condition.

Intermediate Post-Partum Care: The Six-Week Visit. One of the most impressive changes in medical thinking during the past decade is the feeling that each individual practitioner can, thru thoughtful and enlightening discussion with his patients, serve to show them a more healthful way of life. These discussions need not be the source of fear and apprehension on the part of the patient, but rather an opportunity for the doctor to explain the whys and the wherefores of medical practice (8). The role of the Papanicolaou smear and the periodic pelvic examination in the early detec-

tion of carcinoma of the female generative tract should be discussed freely and openly with our patients. In many cases they will have already been mentally prepared for such a discussion after having read various articles in the lay press. In other cases they will broach subject themselves. Easterday has aptly called the years between 29 and 40 as the 'lost Decade" (9). He stresses that at this time the patient is likely to be busy rearing her family and does not wish to take the time nor the expense for visits to her physician, especially if she is feeling well. Asensio has suggested that this is a perfect time to detect and treat subclinical anemias (10). The elimination of the borderline anemic state will do much to improve the health of the entire family, since a mother who is functioning in a chronic state of distres cannot devote as much time and attention to the welfare and the needs of her loved ones.

The Pelvic Examination. The pelvic examination is a part, but not the only part of the care given in the intermediate post-partum period. The breasts must not be neglected, even if the patient is lactating. It should be remembered that the lactating breast may present with some nodularities, but any suspicion of cancer shoul be investigated by routine means.

It cannot be emphasized too strongly that the patient should be undressed of all her clothing and covered with a sheet or suitable gown during the examination. Modesty on the part of the patient and undue haste on the part of the physician have both been known to contribute to the failure to detect an abviously malignant lesion. The female undergarments are not constructed to aid in either the visualization or the palpation of anatomic structures. A good light source is mandatory.

The Papanicolaou Smear. It is unfortunate that there are still physicians who are either skeptical about the value of the Papanicolaou smear or simply refuse to use it. This is tragic because there is absolutely no sense in waiting till cervical carcinoma becomes obvious to the maked eye to institute its diagnosis and treatment. These physicians argue that on the basis of their clinical experience they can tell what a normal cervix looks like, but in truth they cannot rule out incipient carcinoma with their eyes. Many a cervix which appears entirely normal is constantly exfoliating malignant cells into the vagina where they lie awaiting removal by normal processes, by the use of a douche, or by becoming part of the Papanicolaou smear which is destined to save the patient's life. Since none of us can guess which of all the myriads of normal appearing cervices is the culprit, it must become a rule to take a smear in every post-partum patient regardless of her age and parity or her ability to pay for this herself.

The technique of obtaining the smear is simplicity itself. The speculum, unaided by any lubricating agent other than water, is introduced into the vagina. A regular tongue blade or the specially constructed Ayer Spatula may be used. A cue-tip will do in the absence of these materials. The vaginal pool is sampled for the first part of the slide, and then the cervix itself is circumferentially scraped using another blade or spatula. The reason for doing it in this order is to prevent any bleeding which might be occasioned after the cervical manipulation from interfering with the quality of the sample from the vaginal pool.

The classic and lifelong investigation of Dr. Georges Papanicolaou culminated in his proposing a classification for the exfoliated cells from the cervix (11). The intelligent interpretation of the smears allows the physician to say with a fairly certain degree of accuracy either that a malignant condition is not present o rthat other diagnostic procedures must be instituted to rule it out. Certain cytopathologists have refined the process to the state that they will state that the patient has carcinoma in situ, invasive squamous cell carcinoma in situ, invasive squamous cell carcinoma or adenocarcinoma of the cervic. However, in the main, the reports of any given smear will be in the original five classes of Papanicolaou: Class I-Negative, Class II-atypical benign (often with infection), Class III-suspicious, Class IV-probably positive, Class V-definitely positive for cancer. If a report reads Class III, IV, or V a repeat smear should be obtained as soon as possible. However, if an infection of the cervix or vagina is present, this latter condition should be actively and vigorously treated before obtaining the second set of smears. It is not an infrequent occurrence that the abnormal cells responsible for a given classification in an individual patient are due

to a severe inflammatory process. There is no question as to the value of the smears in the early detection of carcinoma in situ of the uterine cervix or the invasive variety thereof; approximately 25% of patients with Class III, 75-80% of Class IV, and an even higher percentage with Class V have either carcinoma in situ or invasive cancer (12). Smears should be repeated twice within a year if this is the first time that they are being done and every year thereafter. Such a system of coverage is adequate to discover lesions as they develop (13).

The Schiller Test. This test, when properly performed and interpreted, alerts the clinician to the possibility of premalignant lesions and carcinoma in situ in about 80% of cases where the cervix is normal appearing. It is not and will never be a replacement for the Papanicolaou smear from the point of view of mass screening techniques. The test is essentially the application of an iodine containing dye to the cervical and vaginal epithelium. Normal cells in this area contain glycogen and take up the stain turning a dark brown. They are called "Positive". The "Schiller negative areas" are areas of *squamous epithelium* which do not take up the stain. The glandular epithelium which is involved in an "erosion" is normally negative and cannot be expected to take up the stain. It is well known that carcinoma in situ almost always arises near the squamo-columnar junction. In 90% of the cases the nearby squamous epithelium is either involved or there is an associated dysplasia, hyperkeratosis or leukoparakeratosis. These are the conditions which normally give rise to a "positive" Schiller area and which need to be biopsied.

The test may be done after the Papanicolaou smear has been taken. The portio of the cervix should be cleansed using a solution of 1:1000 aqueous zephiran on a cotton swab. Shiller's reagent (one part iodine, two part potassium iodide, and 300 parts of water) may be swabbed on with a cotton pledget or sprayed on using a 2 cc sryringe and 25 gauge needle as a spray gun. In a moment or two the normal areas have taken up the stains and the areas in question may be submitted to biopsy.

Cervical Biopsy. Unless an obvious lesion is present, we do not use a roundjawed biopsy punch because this often has the tendency to slip and one winds up either with a gigantic bite or tearing out a piece of the cervix. A sharp squarejawed biopsy forcep is preferable especially if one of the jaws has teeth to grasp into the cervical epithelium. Several radial biopsies may be necessary to include all the Schiller positive area and they should be labeled as to the positions on the face of a clock and submitted separately if at all possible.

Intermediate Post-Partum Care: Cervicitis — Its Significance and Treatment

Cervical Infections. Patients vary greatly in their ability to tolerate cervical infections and the symptoms that they produce. All of us who treat women have at times been confronted with a patient who complains that her undergarments have a slight stain only to be followed by another whose constant leukorrhea requires the use of a sanitary napkin; in the latter instance, however, the patient accepts this as part of her lot in life.

Infection comes as easily to the cervix as it does to the tonsil. Its anatomic location and lymphathic drainage are such that it is frequently implicated as the inciting cause of infections in other pelvic organs. The entire urinary tract is especially susceptible to this type of spread.

The elimination of the acute and the chronic infection in the cervic appears to have beneficial influence in the prevention of the subsequent development of carcinoma. To be sure, this does not imply that the latter condition is due to the former, but only states that the incidence of malignant change is much less in those cervices which have been restored to normal after infection or trauma.

Types of Cervical Infections

1. *Foreign body cervicitis.* In the intermediate post-partum period this is generally an iatrogenic condition in which a sponge or tampon was inadvertently left in the vagina at the time of the episiotomy repair. The patient complains of a profuse, foul discharge, Removal of the offending agent and the use of vinegar or potassium permanganate douches (1:5,000) will help to clear up the condition.

2. *Trichomonas vaginalis vaginitis and cervicitis*: This condition commonly exacerbates during or after pregnancy. Pruritus and leukorrhea are noted by the patient. Examination reveals a characteristic greenish foamy discharge and multiple red spots on the vaginal and cervical mucosa. Diagnosis is made by a hanging drop microscopic examination. Treatment is with Flagyl ®. The husband is considered to be a carrier of the organism and should be treated in recurrent or persistent infections (14).

3. *Monilial cervico-vaginitis*. Pregnancy is one of the common inciting factors in the incidence of this infection. The causative agent is the yeast, *Candida albicans*. The patient complains of severe pruritus vulvae and vaginae associated with leukorrhea and urinary symptoms. Inspection reveals a fiery red vaginal and cervical mucosa with isolated grey-white plaques which are easily wiped away by a cotton applicator. Diagnosis is confirmed by the presence of mycelia in the vaginal smear. Mycostatin ® or one of the other fungicides is the therapy of choice.

4. *Cervical gonorrhea*. In this case the examiner may note the simultaneous involvement of the urethra, Bartholin glands and/or the Skene's ducts. Gram stain of the discharge reveals gram-negative intra-cellular diplococci. The drug of choice is penicillin if the patient is not allergic to it. Other antibiotics are equally effective.

5. *Cervical syphilis*. Luetic infection must always be considered where there is an ulcer with smooth edges on the cervix accompanied by inguinal adenopathy. In the primary stage the serology is not always positive, but dark-field examination will reveal the causative agent, *Treponema pallidum*. Treatment is with penicillin or other antibiotics. Every case of infectious syphilis must be referred to the local public health unit for epidemiologic interviews (15, 16).

6. *Condylomata acuminata*. These commonly ocurring wart-like papillary excresences are found on the vulva tissues, the vaginal mucosa and occasionally on the cervix itself. Their size may vary from very small growts to larger lesions which may fill the vaginal canal or distort the appearance of the external genitals. They are associated with a profuse discharge, but are not ,as formerly thought, the result of this discharge. The causative agent is definitely one of the viruses. The condition is markedly accentuated by pregnancy, and if treatment is not given during the antepartal period the lesions may be present at the time of the six-week-check-up. They may be confused with malignant conditions, but biopsy will substantiate the diagnosis. The therapy of choice is Podophyllin (25% in tincture of benzoin) for the smaller lesions. Occasionally surgical resection must be resorted to. It is wise to caution the patient to wash the medicine off after about two hours to prevent the occurrence of a burn to the normal tissues. More than one application may be required.

Delayed Post-Partum Care: The Three Month Visit

At the time of the three month visit, the physician is able to have before him the result of the Papanicolaou smear, the report of the biopsy (if taken), and the statements of the patient as to her general welfare. He is likewise able to see the effect of any treatment which may have been prescribed for the cervicitis.

If all is well, this is an excellent time to cauterize the cervix to eliminate any resistant foci of infection and restore the squamo-columnar junction to its normal integrity. This procedure is quite simple and may be carried out in the office or the outpatient department of the hospital with minimal discomfort to the patient. As the cervix is generally devoid of sensory nerve fibérs, anesthetic procedures are usually superfluous. There is an occasional patient, however, who might be benefited by the use of a paracervical block or some mild sedation.

The patient should be cautioned that she may experience the sensation of warmth or heat and that she should not move. The cervix is exposed with a bi-valve speculum and the mucus cleaned away either with a cotton applicator or by the application of Caroid solution. In the meantime the cautery should be tested. The production of a dark, cherry-red color is sufficient, but it is wise to hold the electrode in a position so that the patient cannot see it. When the cautery tip has been cooled by dipping it in water, it is inserted

into the endocervical canal approximately to the level of the internal os. The current is then turned on, and the tip brought into contact with the cervix at about 12 o'clock. The operator feels a fine vibration and notes that the tissue is being coagulated and turning a yelowish-grey color. The electrode is then shifted to the three, six and nine o'clock positions where the same procedure is repeated.

After this has been completed, attention is turned to any areas of ectropion or eversion which are touched with the tip of the cautery until the same effect is produced. Any obvious Nabothian cysts are punctured and destroyed. Generally there is no significant bleeding or oozing, but a small piece of Oxycell ® may be used should this occur.

The patient should be specifically cautioned to expect a fairly profuse discharge in the ensuing two weeks. Likewise, it is wise for her to abstain from sexual intercourse or douching for the same length of time. In order to prevent the occurrence of cervical stenosis after cautery, the cervix should be dilated at regular intervals, the first return visit being about one week later. A probe or small Hegar dilator may be used to break up any adhesions. Complete healing takes about three months. Dilatations may be continued at weekly intervals for the first 4 to six weeks.

Summary

Our management of the post-partum cervix is such that:

1) A speculum examination is performed during the pre-natal course, preferably early in the gestation, midway during the pregnancy, and shortly before term. A Papanicolaou smear should always be done at one of these examinations. Appropriate biopsies are done as indicated.

2) The cervix is visualized after the delivery and all lacerations of significant size are sutured whether they are bleeding or not. Any suspicious areas are biopsied.

3) At the six-week examination the Papanicolaou smear is repeated and medicine prescribed for specific cervical infections if present. Biopsies may be taken if indicated.

4) Three month after the delivery the cervix may be cauterized if all previous examinations have been negative for malignancy. We feel that this latter procedure may be responsible for decreasing the possibility of future carcinoma.

Resumen

Manejamos las anormalidades del cuello uterino del período post-parto del siguiente modo: Hacemos exámenes con espéculo durante el período pre-natal, temprano y a mediados de la preñez, y poco antes del término. Tomamos en ellas una prueba de Papanicolaou y biopsias según fueran indicadas. Después del parto, visualizamos bien el cuello y toda laceración importante se sutura, aún cuando no presente hemorragia. Además, se sacan biopsias de cualquier área sospechosa. Repetimos el Papanicolaou en un examen seis semanas postparto, tratamos cualquier infección del cuello que se encuentre y tomamos biopsias si están indicadas. Se puede cauterizar el cuello 3 meses después del parto si todos los exámenes previos han sido negativos. Creemos que este último procedimiento puede disminuir la posibilidad de carcinoma en el futuro.

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WHAT IS WRONG WITH FEE SPLITTING? *

John H. Budd, MD

It is hard to capture in words, rules whose origin must be in the heart, and whose application must be governed by the conscience. Samuel Johnson declared it to be one of the maxims of civil law that definitions are hazardous,[1] and the statement applies equally to moral codes, where the intent of the law is so clearly more important than the letter of the law.

Although medicine is much older than Christianity, and ethical principles for medical practice were conceived about 2500 BC by the Babylonians, there is still no immutable system of rules of ethics comparable to those of mathematics or the natural sciences. Fundamental principles regarding moral conduct have not changed, but it is necesary periodically to review and adjust the code to meet changing concepts and new situations without lowering the basic standards of integrity, the hallmark of an honorable profession.

Fee splitting is condemned in all codes of medical ethics. Bribery is dishonorable, and fee splitting in its most obvious form —the acceptance or payment of a commission for referral of a patient— is bribery; so also is acceptance of a rebate from a pharmacist, brace maker, optician, or other supplier or manufacturer in return for referral of prescriptions. The Judicial Council has adjudged that sharing by two or more men in a fee paid by a patient and presumed to be reimbursement for the services of one man alone is fee splitting.[2] These situations are clear-cut, black-on-white, and unambiguous; they are violations of professional integrity and they are unethical.

There are, however, gray areas, where "circumstances alter cases," and where prejudgment of specific situations is both unwise and unjust.

The division of a fee between a surgeon and his assistant has been declared ethical if the assistance is necessary, is actually rendered, is competent, and if the amount paid for such assistance is commensurate with the service rendered.[3] The assistant may be the referring physician, and the fee may come from the patient or from an insuring agency. In my opinion, informing the patient of the arrangement is also desirable. If, on the other hand, the

* *Reprinted from JAMA,* 195; 161, 1966.

assistant's fee is an inducement for referral, or a bounty in disguise, the practice is unethical.

It seems logical to apply the same rules in considering the reduction of a surgical fee so that the referring physician may collect a fee commensurate with his services. If proposed or transacted as a commission or bride, it is improper; but, under the circumstances specified concerning a justifiable assistant's fee, the arrangement may be above reproach. Here again, it would seem prudent to inform the patient of the plan, and the rendering of separate bills would be particularly important as reassuring evidence of honorable intent.

The sharing of a physician's fee with a hospital is a corrupt practice if it is a requirement for hospital privileges or staff membership.[4,5] Examples of this form of fee splitting are seen in the bed tax or admission assessment, in the compulsory rebating of insurance benefits by the physician to the hospital from patients adjudged to be staff cases who have medical-surgical insurance coverage, and in the enforced restriction of income from consulting or other private-practice activities by full-time teaching faculty members in university hospitals, with the excess over the stipulated income limit passing to the hospital. Compulsion seems to be the unethical distinguishing feature. It has been declared policy by the House of Delegates that "a physician should be the sole arbiter of the ways in which he shall dispose of his professional earnings, consistent with the laws of the land and the principles of medical ethics." [6] After having received payment for his services, a physician may voluntarily make such donations from this income as he wishes. I believe he should actually receive the reimbursement himself and the reassign it if he wishes, and the preferred depository for such rebates would be a fund administered by the physician and his professional colleagues, and disbursed according to their wishes.

Sharply debated, and several times altered, have been the terms under which it is ethical for the reimbursement of hospital physician specialists to be a percendepartment concerned. It was stipulated by the House of Delegates in 1951 that it is unethical for a physician to dispose of his tage of the billing or of the income of the income "under terms which permit the sale of these services by a hospital for a fee." [7] This was modified in 1953 "to recognize the right of an individual to develop terms of his service on the basis of local conditions and needs," [8] and the unacceptable contractual terms were more moderately defined: the sale of services of a physician were pronounced free of unethical taint provided there was "no exploitation of patient, hospital or physician." This milder statement was revoked by a reaffirmation of the 1951 proclamation,[9] so that now again it is clearly considered to be unethical for a hospital or other corporation to hire a physician and then sell his services for the profit of the corporation.

As more and more categories of physicians' services become hospital based, it becomes increasingly important that these functions be recognized as physicians' services and not hospital services. It is my opinion that separate billing by the physician helps to maintain this distinction, and that, failing this, at least identification of the physician and his fee should appear on the hospital bill presented to the patient.

The method or basis of fee division between various members of a group or clinic may be entirely unexplained to the patient. It is secret fee splitting by definition, but is it necessarily dishonest or immoral? I think not. The calling of competent consultants when needed, and with the patient's knowledge of consent, is customary practice and is for the patient's benefit; the fact that he consultants are in a partnership does not disqualify the action. Unnecessary consultation, of course, constitutes exploitation and is obviously reprehensible.

In a group, as contrasted with individual practice, specialists of high earning potential may receive a more limited income as group members when the pooled proceeds are divided with partners in less productive fields. In today's group practice such division of fees is considered morally acceptable and professionally proper. There is no exploitation of the patient, and in such a voluntary organization, free of coercion, the stimulating professional association and the satisfaction derived from the improved quality and availability of comprehensive facilities may be advantages which justify the terms of the partnership, and there is no exploitation of the physicians.

If the department head in a hospital-bound specialty, or a physician in outside practice planning to take on a partner, engages his associate as an employee for an initial specified period, this seems to be sanctioned, honest, and fair if the duration of the employee relationship is limited, if the salary is adequate, if there is no element of coercion, and if the time for advancement to partnership status is defined. If, however, when partnership becomes imminent, the physician-employer routinely and unfairly replaces prospective partners with new starters, the practice constitutes exploitation of a physician by another physician, and this in my judment is as unethical as any other exploitation. again, it is a matter of sincerity of motive; the arrangement should be "devoid of envy, guile, and lust of gain."

Team techniques are necessary for increasingly numerous complicated medical and surgical procedures, such as open-heart operations, organ transplants, replacement of accidentally amputated major extremities, multiple-system diseases and injuries, and artificial-organ management of metabolic crises, to name a few. A considerable number of specialists may be involved, and the problems of allotment of proportionate fees are obvious. The patient or his insuring agency may prefer or, indeed, insist on a single bill, and although ethical principles decree separate bills, concession to social and economic changes suggest compliance in the form of a properly itemized single bill.

With the increase in complexity of medical science, and with the alterations in the relationship of physicians to each other, to allied scientists, to government agencies, to insuring and prepayment plans, to hospital, and to medical schools, these questions on ethical reimbursement will continue to multiply. As we face these questions it should be remembered that the basic relationship is between physician and patient, and the fundamental guide to conduct is moral integrity. Intelligent and uncorrupted application of the principles of ethics and their intent will be rewarded by

the confidence of our patients, the esteem of our colleagues, and, above all, our own self-respect.

> To sit alone with my conscience
> Will be judgment enough for me.[10]

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CASE REPORT

SINDROME DE LANGE
(typus Amstelodamensis)

Héctor Arroyo Scotoliff, M. D.

Desde que Cornelia de Lange en 1933 hizo la descripción del síndrome que lleva su nombre (1), se han presentado hasta el momento, que se conozcan, cincuenta y dos casos en la literatura médica mundial (Tabla I). Con anterioridad Brachmann en 1916 había descrito este síndrome, pero pasó desapercibido, por lo que siendo de justicia debería mejor llamarse "síndrome de Brachmann de Lange". El presente es una nueva aportación del mismo, siendo a su vez el primero en la literatura médica puertorriqueña y, en lo que nos alcanza, en la hispanoamericana. En 1961, P. Altozano (2) publicó el primer caso conocido en un país de lengua española. Hasta 1963 no aparecen los primeros casos publicados en Norteamérica, siendo sus autores Jervis y Stimson (3) por una parte y Ptacek y sus colaboradores (4) por otra.

Algunas de las manifestaciones clínicas del síndrome aparecen en la Tabla II.

Del Departamento de Pediatría, Hospital de Distrito de Fajardo.

Presentación del Caso

Un niño de ocho meses de edad, de raza blanca y último de 15 hijos de padres sanos, nació en el Hospital de Distrito de Fajardo, tras una gestación a término, durante la cual la madre sufrió de "catarro" a partir del tercer mes de embarazo. El parto fue normal, pesando al nacer 3,600 gms. Desde el primer momento llamó la atención por el aspecto especial de su cara, así como por la gran cantidad de pelo que cubría la cabeza y la espalda, y por las malformaciones de los dedos pulgares de las manos y los gruesos de los pies, como consta en su historial.

No presentan ninguna particularidad especial en los antecedentes familiares salvo el hecho de que un primo materno del nacido, presenta una sindactilia de los dedos del pie derecho.

Desde pocos días de nacido presenta dificultad al tragar, episodios de regurgitación, períodos de apnea y cianosis durante la alimentación. A la vez presenta un retraso de desarrollo psicomotor traducido en la imposibilidad de sentarse y en la dificultad en darse la vuelta de echado, cosa esta última que no pudo hacer hasta la edad de siete meses y medio. Tampoco pudo agarrar objetos hasta los siete meses.

A los ocho meses de edad, en la Clínica Externa de Pediatría General del Hospital de Distrito de Fajardo, la exploración presentó el siguiente cua-

dro clínico que nos hizo relacionarlo con el síndrome de Lange (Fig. 1 - Fig. 2): talla, 61 cm; peso



Fig. 1: Conformación corporal a la edad de 8 meses.

4,274 gms; presión arterial 70/50; cabeza braquicefálica con occipucio aplanado de unos 39 cm de circunferencia; cejas pobladas, unidas en la línea media; frente con gran hipertricosis, nariz corta y respingona con puente aplanado (silla de montar). Al examen oftalmológico presentó pestañas largas y curvas (como las estrellas de cine, dicen los franceses); repliegue bilateral de los párpados inferiores; ligera exoftalmia; paresia de los músculos motores; ligera palidez de la papila óptica y miopía, la cual es más intensa en el ojo derecho. También presentaba labios finos; dientes pequeños e irregulares; paladar ojival; orejas pequeñas de implantación baja; maxilar inferior hipoplásico; cuello corto; implantación proximal de ambos pulgares en las manos, los cuales son de forma aplanada y achatada, dando la impresión de sindactilia incompleta (Fig. 3). En la mano izquierda (Fig. 4) presenta además un surco transversal como en el mongolismo. También el dedo gordo de cada pie (Fig. 5) presenta unas características similares a los pulgares de las manos.



Fig. 2: Braquicefalia, occipucio aplanado, nariz respingona, orejas de implantación baja y cuello corto.



Fig. 3: Pulgar grueso, aplastado de implantación proximal.

Tanto la percusión y auscultación pulmonar y cardíaca, así como la exploración abdominal fueron negativos.

El hemograma y el examen de orina fueron normales. Calcio 9.6 mg/ml; cloruros, 112 meq/L; fósforo, 5 mg/100ml; potasio, 5 meq/L sodio, 143

meq/L; nitrógeno uréico, 17.5 mg/100 ml.; colesterol, 134 mg/100 ml; captación tiroides de iodo radioactivo, 7.1%.

Por falta de facilidades técnicas, nos ha sido imposible realizar los estudios cromosómicos en nuestro paciente.



Fig. 4: Surco transversal de la palma de la mano.



Fig. 5: Forma ancha y aplanada de los dedos gruesos.

No se revela en el exámen radiológico, retraso en la edad ósea. Las radiografías de mano y pies demuestran la existencia de los siguientes hallazgos: 1) La falange proximal del dedo gordo de la mano derecha tiene forma semilunar. 2) El dedo pequeño del pie izquierdo presenta su falange proximal normal, pero la distal, se encuentra sustituída por dos puntos de osificación; a su vez, al dedo grueso del mismo se le aprecia una falange distal doble, mientras que el derecho la tiene bífida. (figura 6, 7 y 8).



Fig. 6: Radiografía de mano derecha donde se aprecia la falange proximal del pulgar de forma semilunar.



Fig. 7: La falange distal del dedo grueso del pie derecho presenta forma bífida.



Fig. 8: La falange distal del dedo pequeño del pie izquierdo está sustituída por dos puntos de osificación, y el dedo grueso presenta su falange distal doble.

Comentario

Con las recientes aportaciones de Ptacek y col. (4), Geudeke y col. (5), Silver (6), Hart y col. (7), y la nuestra, más bien simultaneas, que suman un total de 53 casos, nos hace pensar que este síndrome dista mucho de ser considerado como raro, tal cual se le creyó originalmente. Aparentemente es pasado por alto, o se le etiqueta bajo otro diagnóstico.

Los estudios cromosómicos realizados han dado resultados dispares: por un lado Laurence e Ishmael (8), Giraud (9), Heinz (10), y Ptacek y col. (4) encontraron cariotipos normales; mientras que Schlensinger (11) en uno de sus dos pacientes halló una posible variación en los satélites de los grupos 13 y 15. Igualmente Jervis y Stimson (3) encontraron una fragmentación en 4 de sus cinco casos presentados y Geudeke (5) reportó traslocación entre los cromosomas 5 y 22 en uno de sus tres casos.

Se han descrito una gama de anomalías unidas a este síndrome, tales como; cardiopatías congénitas (Richter (12), Zunin (13) y Jervis y Stimson (3); hipertelorismo (Arnaud-Battandier y Gillot (14), Bardier y Degoy (15); hipospadia (12); estenosis de piloro (Laurence e Ishmael (8); malformaciones asimétricas de las manos (4) y (14); ectrosindactilia (6); útero bicorneo (4); retardo mental; hipertrofia muscular generalizada.

Los estudios necrópsicos realizados han sido muy pocos (1, 6, 11, 12), siendo el primero verificado por de Lange en su primer caso, el cual murió de trombosis de los senos cerebrales a la edad de 6 años. Todos ellos presentan anomalías en el desarrollo cerebral, tales como atrofia de la corteza cerebral, microencefalia, y en otros, malformaciones cardíacas y del tracto intestinal. Recientemente Bjorklof (16) presenta un caso con quistes de Ratke en la glándula pituitaria, el cual produjo por compresión una hipoplasia de los lóbulos anteriores y posteriores.

Los pacientes del typus Amstelodamesis. al igual que los afectos con el mongolismo o síndrome de Down, tienen un aspecto muy característico y de familia que los hace fácil de reconocer; si bien las anomalías que presentan pueden encontrarse en otras entidades que también van asociadas con retraso mental:

a) Gargolismo o síndrome de Pfaulander y Hurler-ambos presentan retraso estatural e intelectual, pero no aparece en el de Lange ni la hepatomegalia ni los trastornos

en los mucopolisacáridos, así como los gránulos de Reilly's.

b) Mongolismo si bien presentan un conjunto, retraso mental y estatural es este una aberración cromosómica.

c) Cretinismo — en este hay alteración en el colesterol y en el yodo unido a las proteínas (P.B.I.).

d) Con la displacia ectodérmica, se diferencia por la ausencia de entolerancia al calor.

Ya hemos expuesto previamente la disparidad de los estudios cromosómicos lo que nos lleva a descartar la posibilidad, como causa patogenética, de una aberración cromosómica. Igualmente puede descartarse la consanguinidad, así como la edad de los padres y el orden de nacimiento.

El proceso patogénico debe ocurrir en o antes del estadío de los 8 - 10 mm.

A partir de sus estudios, Opitz y col. consideran como causa etiológica la herencia autosómica recesiva, basándose en las siguientes razones:

a) síndrome de múltiples anomalías (síndrome de Ellisvan Creveld y de Lawrence — Moon — Biedl en el hombre son rara vez heredados como mutaciones dominantes.

b) hasta el presente no se ha presentado ninguna evidencia de causa ambiental.

c) estudios citogenéticos no fundamentan la etiología cromosómica.

Resumen

Se presenta un caso de síndrome de Cornelia de Lange (typus Amstelodamensis) en un infante puertorriqueño que, presumimos, sea el primero descrito en la literatura médica de Puerto Rico. Este síndrome no parece ser debido a alteraciones cromosómicas, aceptándose en la actualidad la herencia autosómica recesiva.

Summary

A case of Cornelia de Lange's syndrome in a Puerto Rican male infant has been presented which to the best of our knowledge, is the first one reported in the Puerto Rican literature. At present the most probable etiology is an autosomal recessive inheritance.

TABLA I: REPASO DE LITERATURA DE CASOS DE SINDROME DE LANGE

Autor, Año	Núm. de Casos	País
de Lange, 1933 (1)	2	Holanda
Vedder, 1935 (17)	1	Holanda
de Langé, 1938 (18)	1	Holanda
Pincherle, 1939 (19)	1	Italia
Marie y col., 1964 (20)	1	Francia
Willemin-Clog y col., 1947 (21)	1	Francia
Keizer, 1952 (22)	1	Holanda
Arnaud-Battandier y Gillot, 1953 (14)	1	Argelia
Borghi y col., 1954 (23)	1	Italia
Pardier y Degoy, 1956 (15)	1	Francia
Zunin 1957 (13)	1	Suecia
Zweymüller, 1957 (24)	1	Austria
Altozano, 1961 (2)	1	España
Richter, 1961 (12)	3	Alemania
Giraud, 1963 (9)	1	Francia
Schlesinger y col., 1963 (11)	6	Ingraterra
Laurence e Ishmael, 1963 (8)	2	Ingraterra
Heinz, 1963 (10)	1	Alemania
Jervis y Stimson, 1963 (3)	5	E.E. U.U.
Ptacek y col., 1963 (4)	9	E.E. U.U.
Geudeke y col., 1963 (5)	3	Holanda
Silver, 1964 (6)	1	E.E. U.U.
Hart y col., 1965 (7)	6	E.E. U.U.
Bjorklof y col., 1965 (16)	1	Finlandia
Arroyo Scotoliff, 1965	1	Puerto Rico

TABLA II: RESUMEN DE ALGUNAS ANOMALIAS DESCRITAS

Antecedentes familiares:
- a) Exposición de los padres a radiaciones roentgenológicas e irradiaciones a isótopos antes de la concepción
- b) Hallazgos anormales similares en los parientes.

Embarazos:
- a) Proceso catarral durante el primer trimestre.
- b) Movimientos fetales débiles.

Período neonatal:
- a) Dificultades al chupar y al tragar.
- b) Períodos de apnea y cianosis.
- c) Períodos de regurgitación y aspiración.

Crecimiento:
- a) Retardo mental.

Generalidades:
- a) Mayor susceptibilidad hacia las infecciones.
- b) Hipotonia e hipertrofia muscular.

Cráneo:
- a) Microbraquicefálico.

Cara:
- a) En forma de máscara y falta de expresión.
- b) Frente baja cubierta de pelo.
- c) Ligera micrognatia.
- d) Aumento del espacio nasolabial.

Ojos:
- a) Cejas pobladas unidas en la línea media.
- b) Pestañas largas y curvas.
- c) Parálisis músculos oculares.
- d) Ligero exoftalmos.
- e) Miopía severa.
- f) Escleróticas azules.

Naríz:
- a) Respingona y pequeña con puente deprimido.

Boca:
- a) Labios finos.
- b) Paladar ojival.
- c) Paladar hendido.
- d) Retardo en la dentición
- e) Dientes pequeños
- b) Pelo fino en el dorso, hombros y extremidades.
- c) Hemangioma cavernoso.

Tronco:
- a) "Pterigium colli"
- b) Cuello corto
- c) Anomalía del ángulo de Louis.
- d) Areolas pequeñas.
- e) Hernias umbilicales e inguinales.

Brazos:
- a) Limitación en los movimientos del codo.
- b) Cortedad en los antebrazos.

Manos:
- a) Línea simiesca palmar
- b) Focomelia y micromelia.

Dedos:
- a) Pulgares cortos y de implantación proximal.
- b) Dedo meñique corto y encorvado
- c) Cortos y afilados

Pies:
- a) Pequeños
- b) Uñas de implantación profunda
- c) Desplazamiento hacia abajo de los dedos 2º, 3º y 4º.
- d) Sindactilia parcial de los dedos 2º y 3º.

Hallazgos radiológicos:
- a) Luxación de la cabeza del radio.
- b) Costillas delgadas.
- c) Retraso en el desarrollo de las epífisis.
- d) Luxación de las caderas.
- e) Clavicula pequeña, la cual no articula en el esternón.

Otras anomalías:
- a) Espina bífida
- b) Criptorquidia
- c) Hernia hiatal

Oídos:
- a) Orejas de implantación baja.

Piel:
- a) Cutis-marmorata.

Agradecimiento

El autor dedica esta aportación al Dr. Ricardo Alonso, antiguo Jefe del Departamento de Pediatría del Hospital de Distrito de Fajardo y actual médico visitante del mismo, por todas las enseñanzas y consejos de la práctica médica y pediátrica en particular.

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EDITORIAL

PALUDISMO

Como resultado del conflicto en Vietnam ha vuelto a surgir en nuestro medio la malaria, enfermedad que ya casi habíamos olvidado. Un grupo creciente de nuestros compatriotas ha estado expuesto a infección por este protozoario, trayendo consigo la enfermedad en su forma latente que una vez aquí viene a manifestarse clínicamente.

La malaria sigue siendo uno de los problemas de salud más importantes de las latitudes cálidas del globo. A pesar de una intensa campaña de control llevada a cabo por agencias nacionales e internacionales, se calcula que sobre un billón de personas viven todavía en áreas endémicas y más de 400 millones habitan regiones donde ni siquiera han comenzado programas para la erradicación de la infección (1). Grandes regiones del sureste de Asia, del centro de Africa y de Sur América permanecen en gran parte fuera del alcance de estos programas. Entre las tropas norteamericanas en Vietnam la malaria es la primera entre las enfermedades infecciosas como causa de tiempo perdido de servicio.

Se desconoce con certeza por qué ruta llegó la malaria a la América desde su probable fuente de origen en Etiopía. Existe evidencia circunstancial de varios tipos —linguística, botánica e histórica,— que sugiere que la malaria vino a este hemisferio en épocas precolombinas (2). No hay duda que el vector estaba a la mano, pues se conservan dibujos de mosquitos en piezas de alfarería de origen prehistórico en Nuevo Méjico. Aunque es posible que la malaria atravesara el Pacífico con los cazadores asiáticos que cruzaron el Estrecho (entonces tierra) de Bering en el Pleistocenio o a través del sur del Pacífico mediante migraciornes de los aborígenes de la Polinesia y Melanesia, es también posible que la malaria fuera traida más tardíamente por exploradores cartagineses, griegos y árabes que conocían la ruta trasatlántica ante de los viajes del Gran Navegante. Se cree, sin embargo, que aunque la enfermedad existiera en América para esa época, se limitó a pequeños focos geográficos debido probablemente a la preferencia de muchos de los grupos indígenas por la altiplanicie donde las condiciones eran poco favorables a su diseminación. Sea éste el caso o no, el influjo de millones de esclavos negros del oeste de Africa después del año 1500 fue responsable del problema de magnas proporciones que constituyó la enfermedad en vastas áreas del Norte y Sur América hasta la primera mitad de este siglo (3).

En Puerto Rico la malaria constituyó uno de los problemas más importantes de salud pública hasta el 1945 (4). Para 1920 aproximadamente el 31% de la población de las regiones costeras de la isla era portadora del parásito. Entre los años 1931 y 1941 la malaria fue causa de muerte de más de 24,000 puertorriqueños. En 1941 se informaron 23,578 casos con 1,817 muertes. Como resultado de un programa intenso de control, ya para el año 1955 la malaria podía considerarse como prácticamente erradicada en Puerto Rico. A pesar del influjo de casos militares durante el conflicto de Corea, no se identificaron casos secundarios. Esto se debió probablemente al gran factor de dilución poblacional que no permite una concentración favorable a la transmisión a pesar de seguir siendo prevaleciente el mosquito Anopheles en muchas áreas de la isla.

Más que un problema de salud pública, la malaria es ahora en Puerto Rico un problema de medicina individual. Además de los casos de origen militar, vemos ocasionalmente casos originados en otras áreas que nos llegan debido a la facilidad de la transportación aérea. Es importante, pues, para el médico considerar esta enfermedad en el diagnóstico diferencial de todo caso de enfermedad febril en individuos que provengan de regiones endémicas y mantenerse al tanto de los adelantos en su tratamiento.

Reproducimos en este número del Boletín una publicación de la Oficina del Cirujano General del Ejército de los Estados Unidos que resume los conceptos más recientes sobre el manejo de esta enfermedad. Se enfatizan allí las varias formas clínicas atípicas en que puede manifestarse y la necesidad de instituir tratamiento rapidamente, especialmente en casos de infección por P. falciparum, la variedad más maligna, que constituye el 90% de los casos originados en Vietnam. Se detallan también las diversas modalidades de tratamiento.

Julio V. Rivera, M. D.

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Guidelines for the management of malaria *

1. Over 90% of the identifiable malaria encountered in Southeast Asia is due to *Plasmodium falciparum* and only a very small portion to *P. vivax*. This suggests rather strongly that the curren chemoprophylactic combined tablet (chloroquine base, 300 mgs; primaquine base, 45 mgs) is effective in suppressing vivax infections and probably a certain number of falciparum infections as well. Furthermore, the fact that the incidence rate of malaria among troops on active combat or patrol duty is several times higher than among support troops based in the same area indicates that environmental control measures are still effective to the extent that the tactical situation permits their application.

2. Falciparum malaria frequently does not appear in the classical form with recurrent attacks of chills, fever, and sweating. Cases have presented with gastrointestinal complaints, musculoskeletal symptoms, postural hypotension, unexplained high fever, irrational behavior and delirium, the latter not infrequently without fever or even with subnormal temperature. *Malaria should be considered in the differential diagnosis of any sick individual who has been in Southeast Asia.* Early diagnosis and initiation of therapy are of utmost importance. Because routine thin blood smears are less apt to show the parasites in falciparum malaria than in other forms of malaria, the use of thick smears is advised whenever the diagnosis of malaria is under consideration. Each smear should be examined for at least 10 minutes before being reported as negative. TM 8-227-2 (reference 1) contains detailed information concerning methodology.

3. In the therapy of *P. vivax* malaria and probably in many cases of previously untreated falciparum malaria, the standard chloroquine regimen as prescribed in TB Med 164, and in the bookled "Control of Communicable Diseases in Man," 10th Edition, 1965, will prove effective. This consists of an initial dose of chloroquine phosphate, 1.0 Gram (two tablets, each containing 300 mgm of base), 0.5 Gram six hours later, and then 0.5 Gram once daily for the next two successive days. (Total dose is five tablets or 2.5 Grams of chloroquine phosphate in three days). If the patient is unable to take or retain chloroquine given orally, the drug may be given as the hydrochloride, 250 mgs intramuscularly, and repeated in six hours, switching as soon as possible to the oral medication. This regimen should be employed initially for patients with any type of malaria who are not critically ill and in whom the record does not indicate that such a course of therapy has already been administered.

4. In patients (a) who are gravely ill, or (b) have not responded to the chloroquine treatment described above, or (c) have a clinical relapse despite a previous response to a course of chloroquine, the treatment of choice is quinine. This is administered as quinine sulfate 1.0 Gram (three tablets of 5 grains each) three times daily for two days, followed by 0.65 Gram (two tablets of 5 grains each) three times daily for the next eight days. Because of a variable tendency to develop postural hy-

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potension, patients should be kept at bed rest during quinine administration. The urine output should be measured and if oliguria develops, quinine should be temporarily discontinued. During oliguria, quinine blood levels rise precipitously and acute quinine toxicity ensues.

5. When the patient is unable to retain quinine, because of vomiting, or when coma, presumed due to falciparum malaria, is present, the drug must be given intravenously. It must be emphasized that this treatment carries a serious hazard and should be resorted to only when the patient's condition clearly warrants the risk and no other form of treatment is possible. Quinine is administered intravenously as the dihydrochloride, 600 mgs in 600 cc of normal saline, by *very slow* intravenous drip over a period of at least 30 minutes with constant monitoring of the blood pressure and of the pulse to detect hypotension or arrhythmia. The same intravenous dose may be repeated at intervals of six to eight hours if the patient's condition requires. Oral therapy, by stomach tube if necessary, should be utilized as soon as possible.

6. Patients who relapse after quinine therapy should be retreated with quinine as described above. If necessary, the course of quinine may be maintained for 21 days at a dosage of 0.65 Grams (10 grains) three times daily, as tolerated.

TB MED 164, June 1959 (currently under revision) may be obtained from Office of the Adjuntant General, 2B Room 2406, 2d and S Streets SW, Attn: AGAM-D, Washington, D. C. 20315

Control of Communicable Diseases in Man, 10th edition, may be ordered at a cost of $1.50 a copy, from American Public Health Association 1790 Broadway, New York, N. Y. 10019

7. In patients who respond clinically to chloroquine or quinine, but in whom asexual parasitemia persists or recurs, the patient should receive a course of pyrimethamine (Daraprim), 50 mgms daily for three days concurrently with sulfadiazine, 0.5 Gram every six hours for five days.

8. Patients treated for malaria by any of the above regimens should be followed for four weeks subsequent to treatment in the medical facility and thick blood smears should be examined at least weekly. In addition, the patient should take the combined chloroquine-primaquine prophylactic tablet at weekly intervals for a total of eight weeks as further insurance against relapse. *Note:* The combined chloroquine-primaquine- tablet should *never* be used for therapy of the acute attack, as the amount of primaquine contained therein (45 mgs) may produce hemolytic reactions when the tablet is administered in this manner. This drug is used *only* to destroy the exo-erythrocytic, or tissue, forms of the malaria parasite in individuals who have been in a malarious area.

9. An infrequent, but serious, complication of falciparum malaria is the occurrence of black-water fever. This is an acute intravascular hemolytic episode with such rapid red blood cell destruction that the reticuloendothelial system is unable to dispose of the pigments. Hemoglobinuria, the cardinal diagnostic sign, results. Opinions differ as to the precise cause of this complication. It is known to occur more frequently in the individual with chronic (or recurrent) malaria due to *P. falciparum*. It appears to occur more frequently in the Negro and, according to some is related to therapy with quinine. It also has occurred in patients receiving primaquine during the acute phase of falciparum malaria. Treatment of black-water fever is essentially the treatment for an acute hemolytic transfusion reaction: Mannitol and hydration to institute and maintain diuresis, alkalinization to minimize the formation of hemo-

globin casts in the kidney and the use of peritoneal or hemodialysis if renal failure occurs. An intravenous infusion should be administered and twenty grams of mannitol (100 ml of a 20% solution) given over 5-10 minutes after the patient has been sufficiently hydrated. If urine flow in the next two hours is under 60 ml per hour fluids should be restricted and the patient treated as for acute renal failure. If urine flow exceeds 60 ml per hour, then hydration should be continued and 100 ml of 20% mannitol administered often enough to maintain a urine flow of 100 ml per hour or more. The patient must be carefully monitored during prolonged mannitol therapy for sodium loss with resultant hyponatremia. Packed RBC should be given if necessary to combat severe anemia. Despite the fact that some authorities have suggested quinine as a possible cause of black-water fever, quinine should be given as described in paragraphs 4 and 5 if black-water fever occurs in the presence of demonstrable parasitemia. Caution should be exercised in determining quinine dosage if the blood urea nitrogen is elevated, since a delay in the degradation of quinine under such circumstances may result in dangerously high blood levels of the drug.

10. It is recognized that there are many drugs other than those mentioned above which have been utilized for the treatment of malaria. These include a variety of drugs directed against various stages of the parasite life cycle. In addition, corticosteroids have been reported to be of benefit to patients with cerebral malaria and may be used in severly ill patients manifesting evidence of adrenal cortical insufficiency or unresponsive black-water fever. The treatment of malaria is receiving constant study and it is entirely possible that other and preferred treatment regimens to those contained in these instructions may be recommended in the future. However, in the opinion of those best qualified to advise, the treatments outlined in this guide are the safest and most effective available at this time.

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UNA SUPLICA AL SENTIDO COMUN

Ha llegado el momento de condenar un hecho, demasiado frecuente en el pasado, motivo de demora en el diagnóstico y tratamiento del cáncer genital femenino. Nos referimos específicamente a aquellas que consultan a su médico por hemorragia vaginal irregular, bien sea durante los años de fecundidad o en la época postmenopáusica. Con demasiada frecuencia el médico se limita a recetar píldoras, tabletas, supositorios, duchas o inyecciones de hormonas sin haber llevado a cabo primero la inspección del cuello uterino con la ayuda del espéculo y mucho menos aún tomar una muestra vaginal para estudio citológico con la técnica de Papanicolaou o hacer un examen bi-manual.

El temor a provocar o aumentar la hemorragia vaginal nunca debe ser razón para prescindir de la visualización por medio del espéculo, que en la mayoría de los casos nos mostrará el área sangrante, por ejemplo, las paredes vaginales, el cuello uterino, o el canal endocervical. La renuencia a practicar este tipo de examen en presuntas embarazadas por temor a influenciar desfavorablemente el embarazo es insostenible, puesto que el trauma del instrumento es mucho menor, por ejemplo, que el del acto sexual, que la mujer ha practicado y probablemente ha de continuar practicando. Toda mujer que está sangrando puede ser examinada en tales circunstancias, excepto en el tercer trimestre del embarazo, época en que condiciones patológicas especiales pueden presentarse y manifestar en forma de hemorragia vaginal.

El resultado neto de esta actitud negativa del médico a examinar una paciente se refleja en que a muchas mujeres con cáncer obvio, clínicamente, se les niega el tratamiento adecuado por períodos de uno a tres meses, e incluso más; una demora que a todas luces disminuye sus probabilidades de sobrevivir. Como no podemos aprobar esta situación, hacemos una apelación a aquellos médicos quienes se enfrentan a toda paciente con hemorragia vaginal. El tiempo y el esfuerzo empleados en un examen ginecológico completo, incluyendo la palpación digital recto-vaginal, serán recompensados por niveles progresivos de salud en estas pacientes, objetivo que todos deseamos y buscamos.

Si en el momento del examen se descubren hallazgos sospechosos, el médico debe referir urgentemente en consulta el paciente al ginecólogo para el diagnóstico y tratamiento adecuado.

Louis Keith, M. D. y
Randolph McConnie, M. D.

THE LONG ASSOCIATION

What other injury can compare with the injured back? It is the nightmare of the insurance carrier, the bane of the patient, the godsend of the malingerer and the dilemma of the doctor.

It may begin with a sneeze or a fall, or a pull or a mistep. It may last an hour or a lifetime. It may be just a simple muscle strain or may lead to herniation of a disc. The patient may limp, have his spine tilt, lose muscle bulk and lose sensation in his limbs. Because it has to do with the spine it produces annoyance in some and terror in others. It is used by some as a good reason to shed responsability and by others as a means of support. It is a condition that brings out the character of a man, his honesty, his avarice, his cunning, his courage.

Through all this the doctor has to sift truth from fiction. He listens carefully to the injured worker's story and examines him. A normal lumbar curve with no detectable lumbar muscle spasm, yet mild palpation produces a painful response. Some limitation of forward bending and straight

leg raising with questionable Lasegue. Normal reflexes and suggestive weakness of the extensor hallucis longus. How much of this is real? How much is the patient putting on? Bed rest for several weeks with or without physiotherapy.

The patient returns, is a little better but not well enough to return to work. So the treatment is repeated. Five months later the same pictures exists. Suggest a lumbo-sacral belt. It helps a little bit, several months later the patient still says he can't return to work. And with somewhat of a shock you realize that eight months have passed and there has still been no commitmet.

So you write that this patient may have an H.N.P. and suggest myelography, which turns out to be negative. You have learned a lesson.

The next patient comes with a similar picture. After six or seven months you decide that the physical findings do not warrant the patient's complaints and suggest the patient return to his previous job. He gives it a try and returns with the same complaints. To prove that he is exaggerating and you are right, you do a myelogram and find a large herniated disc. Surgery is indicated and the patient wants a guarantee that he will come out perfect. After suggesting that he be satisfied with a 75% result, the patient says he is a family man with seven children and must consider it carefully. He returns and decides against taking the chance.

Two months later he returns again, this time belligerent. He was adjudged a small percent incapacity on the State Insurance Fund because he refused surgery. It is explained to him that this examiner has nothing to do with the incapacity determination. He is not salaried by the State Insurance Fund. The patient returns several months later with a letter from a lawyer and a date to appear before the Industrial Commision. Judgement is upheld. Surgery is suggested by the court. Eighteen months have now passed and the patient returns this time with more pain in the leg and wishes the operation. You praise his good judgement and remove a large herniated disc, and completely decompress the nerve and even partially unroof the foramen just to be sure.

Two weeks later the patient feels better. He is grateful and says he wishes to go home; his wife is sick. He returns several times for check-up and actually shows good clinical improvement. Finally it is decided the patient has had a good result from surgery and you tell the now friendly patient this is the last visit and he is to go back to the main office of the Fondo del Seguro de Estado. Two month later the patient returns, using one or two canes or one or two crutches. He is worse. Much worse than before surgery and his accompanying relative hands you a letter which states the patient was given only an incapacity of 30%. There is no change for the worse on examination. The patient is unfriendly again and you wonder how much damage his talking did while waiting his turn in the waiting room. Then you stop to think — Is it worth all the frustration? Certainly not money-wise. Perhaps it is best not to accept these cases and avoid this frustrating two year association.

Then you remember the many workers that have been helped, especially after financial settlements are made, that have returned to work, that are better, and the many more to come who need help and should not be denied. So the average two year association begins again and again.

Nathan Rifkinson, M. D.

NOTICIAS

Locales

BOLETINES VIEJOS

La Asociación Médica de Puerto Rico está interesada en obtener copias de los siguientes números del Boletín:

Años	*Meses*	*Años*	*Meses*
1903	enero a diciembre	1921	enero a diciembre
1904	" " "	1922	" " "
1905	" " "	1923	" " "
1906	" " "	1924	" " "
1907	" " "	1925	" " "
1908	" " "	1926	" " "
1908	" " "	1927	" " "
1911	" " "	1928	" " "
1912	" " "	1942	" " "
1913	" " "	1943	" " "
1915	" " "	1944	" " "
1917	" " "	1953	abril, junio y agosto
1918	" " "	1956	enero a diciembre
1919	" " "	1957	agosto
1920	" " "	1962	julio

Aquellos miembros de nuestra matrícula que tengan estos volúmenes y deseen donárselos a la Asociación Médica, favor de comunicarse con el Sr. Eulogio Bermúdez Vélez, Secretario de Redacción.

ESTUDIO SOBRE CANCER

El Dr. Isidro Martínez, Director del Registro Central del Cáncer del Departamento de Salud ha recibido un donativo del Instituto Nacional del Cáncer para llevar a cabo un estudio epidemiológico de todos los casos de cáncer del esófago, faringe y cavidad bucal diagnosticado en Puerto Rico durante el año 1966.

Muchos de estos casos son atendidos en hospitales privados y por sus médicos privados. El doctor Martínez solicita la cooperación de todos los médicos autorizando a los entrevistadores que le asisten en este estudio a acercarse a los pacientes.

Julio 31, 1966. Convención Semianual de la Sociedad Médica del Distrito Este de la AMPR en el Holiday Inn, comenzando a las 10:30 a. m. Panel sobre Hipertensión.

PSYCHIATRY RESIDENCY

Psychiatry Residency Training is available to qualified physicians with licenses to practice in Puerto Rico. This training program is fully accredited for 1, 2, or 3 years of Psychiatry Residency. Training takes place on the 193-bed Psychiatry Service of a 920-bed general Veterans Administration Hospital in metropolitan Boston, Mass, and in 5 university-affiliated Outpatient Clinics for adults and children. Full range of treatment resources offered by excellent full-time, part-time and consultant staff. Starting salary up to $12,510, per year, depending on qualifications and experience. Write: Dr. David M. Holmes, VA Hospital, 150 So. Huntington Avenue, Boston, Mass.

DEVELACION DE LA ESTATUA DEL DR. ENRIQUE KOPPISCH

El 25 de enero de 1966 se develó la estatua del doctor Enrique Koppisch en la Escuela de Medicina. En dicha ceremonia pronunciaron breves dedicatorias el Presidente de la Universidad de Puerto Rico, Sr. Jaime Benítez, el Cónsul General de España en Puerto Rico, Sr. Ramón Ruiz del Arbol, y el Presidente del Capítulo de la Escuela de Medicina en Puerto Rico de la Asociación Médica Americana de Estudiantes, Sr. Aníbal Marín.

El Sr. Aníbal Marín hizo entrega de la estatua pronunciando las siguientes palabras:

"Señora viuda del Dr. Koppisch, Señor Rector, Señor Decano de la Escuela de Medicina, Distinguidos profesores y visitantes, compañeros:

"El joven Angel Luis Rivera Ortiz, actual Presidente de la Clase de Medicina de 1966, me ha solicitado que haga entrega a la Sra. doña Cristina Soler Vda. de Koppisch, a la Universidad de Puerto Rico, representada por el Señor Rector, don Jaime Benítez, y a la Escuela de Medicina, representada por su Decano, Dr. Adán Nigaglioni, de esta estatua que los estudiantes que componemos la clase graduanda de medicina de este año hemos erigido para honrar la memoria del insigne doctor puertorriqueño, Enrique Koppisch.

"De antiguos discípulos y amigos suyos, los doctores Ramón Suárez y Lorenzo Galindo, entre otros, nació la idea de que se reconociese la labor prominente del Dr. Koppisch. Así lo comunicaron en febrero de 1962 a nuestra clase de medicina, quien acogió la idea sugerida por ellos. La cooperación de distinguidas personalidades y entidades de nuestra comunidad, de doctores amigos suyos, de su ayudante, Sr. Antonio Puras, de profesores y estudiantes, hizo posible el que la idea de los doctores Suárez y Galindo se plasmara en este monumento que hoy les presento. La clase da las gracias a todos cuantos colaboraron en esta actividad, y en especial agradece la cooperación espontánea y desinteresada del Dr. Angel Rodríguez Olleros y la del artista, el escultor español don Pablo Serrano. Honremos, pues, al Dr. Enrique Koppisch, quien en la historia de la medicina en Puerto Rico ocupa un sitio prominente por la calidad de sus logros en el campo de la patología, que ejerció con dedicación exclusiva".

El Presidente de la Universidad de Puerto Rico, Sr. Jaime Benítez, resumió la vida y logros académicos del finado. Citamos de su discurso:

"Hoy recibimos en la Universidad la estatua de alguien que supo ganarla—la estatua en recuerdo del Doctor Enrique Koppisch Cardona, quien empezó a trabajar en este mismo recinto como Instructor en Medicina Tropical el 2 de julio de 1923 y continuó vinculado a ella hasta su muerte el 10 de abril de 1961. Nacido en Mayagüez en 1904, de padre norteamericano y madre puertorriqueña, Enrique Koppisch cursa sus estudios de primaria y secundaria en Aguadilla y de premédica en la Universidad de Puerto Rico. Pasa luego al Jefferson Medical College, donde se doctora en Medicina en 1927. Al terminar su internado en el Hospital Presbiteriano, inicia sus trabajos en nuestra Escuela de Medicina Tropical, recibe entrenamiento postgraduado en la Universidad de Johns Hopkins, en el Instituto Rockefeller de Nueva York, y como "Fellow" de la Fundación Rockefeller en la Universidad de Basilea, Suiza. Pertenece destacadamente al grupo de jóvenes médicos puertorriqueños que para esa época centró su entusiasmo en la investigación de las causas de las principales enfermedades tropicales e imprimió a nuestra Escuela de Medicina Tropical y a través de ella al ejercicio de la Medicina en Puerto Rico, un sello de alta exigencia científica, escrupulosa integridad profesional y prestigio internacional. Este grupo, constituido entre otros por Pablo Morales Otero, Arturo Carrión, Ramón Suárez, Juan Antonio Pons, Oscar Costa Mandry, José Noya Benítez, Federico Hernández Morales, Américo Pomales, Conrado Asenjo y José Oliver González, contribuyó notablemente al esclarecimiento de problemas médicos relacionados con el esprú, la malaria, la brucelosis y la lepra. Enrique Koppisch hizo sus principales aportaciones en el estudio de la bilharzia, el tifus exantemático y en diversas fases de su particular especialidad, la patología.

"Se cuenta, por tanto, entre aquellos médicos que además de servir a la ciencia, han colaborado en poner a la ciencia al servicio del hombre de esta tierra. Por eso merece el reconocimiento de los nuevos equipos de jóvenes médicos que se han beneficiado y continuarán beneficiándose de su trabajo creador y de las normas de conducta profesional que imprimió a su disciplina. Por eso merece la gratitud de la comunidad puertorriqueña y merece que su recuerdo se mantenga vivo no sólo en los laboratorios y en los textos, sino también en la expresión artística. La hermosa obra del escultor español Serrano es testimonio de que así ha de ser. Esta estatua de Koppisch acompañará a los alumnos estudiantes de Medicina, ahora aquí donde trabajó él toda su vida, y luego en el nuevo Centro Médico próximo a erigirse en Río Piedras. Se convertirá en una visión familiar en el recuerdo de las alegrías, ensueños y vicisitudes de los jóvenes en su paso por esta escuela. Agradecemos este donativo. Lo recibimos en reconocimiento a la deuda de la ciencia, de la medicina y de la enseñanza con Enrique Koppisch. Simbolizamos en este monumento la continuada vivencia no sólo del Dr. Koppisch sino también de los otros médicos y

científicos presentes y ausentes que, compañeros suyos, ayudaron desde la Escuela de Medicina Tropical a sentar las sólidas bases y los altos objetivos que informan la investigación, la docencia y el servicio a que está comprometida la Escuela de Medicina de la Universidad de Puerto Rico".

El Cónsul de España en Puerto Rico, don Ramón Ruiz del Arbol, expresó su gratitud hacia el doctor Koppisch por la ayuda y afecto ofrecida por él a los galenos españoles que visitaban nuestra isla. Citamos de su discurso:

"Permitidme que en mi calidad de Cónsul General de España en Puerto Rico, pronuncie unas palabras ante la escultura que mi compatriota Pablo Serrano ha realizado del Dr. Enrique Koppisch. Un grupo de sus amigos puertorriqueños y españoles, bajo la autoridad del Rector de la Universidad y del Decano de la Escuela de Medicina, ha querido perpetuar en maravillosa efigie a un prominente médico, honra de esta isla y honra de su estirpe. Ha querido con la inauguración de esta estatua dejar constancia, a las generaciones que van sucediéndose en el devenir de los años, de la personalidad señera de un sabio y de un hombre de bien. Sus conocimientos médicos, puestos de relieve en este acto, le llevaron a los cargos más sobresalientes. Yo no voy a incidir en ellos, suficientemente conocidos y señalados por personas más doctas. Pero sí debo hacer público reconocimiento de una hombría, de una amistad, de una ayuda que siempre prodigó a los profesores españoles, a los conferenciantes, a los médicos recién llegados a esta tierra desde la España que él supo amar y comprender.

"Koppisch sabía que la vida para unos se hace corta; para otros, larga. La vida—pensaba como el español Séneca—no tiene dimensión si la sabemos aprovechar, y no quiso que fuera desaprovechada en modo alguno la vida y la ciencia de los médicos españoles atraídos por la fuerza de la raza a practicar, con su amor a la carrera, el amor al prójimo. Al erigir, pues, este magnífico monumento, no podían estar ausentes, material ni moralmente, aquellos que fueron sus amigos. Ha cabido también el honor de que este bellísimo monumento fuera concebido y ejecutado por un escultor español. Puedo decir que Pablo Serrano se ha superado, ha puesto toda su alma de artista en la realización de una obra que tiene tanto de interior sentimiento como de correspondencia española. Ante ella, encuadrada perfectamente en el marco de esta culta y famosa Universidad de Puerto Rico, un grupo de españoles, con su Cónsul General, se inclinan con respeto ante la memoria del Dr. Koppisch y rezan ante su imagen una oración de gratitud con cordial y sincera devoción".

El Dr. Angel Rodríguez Olleros expresó las gracias a la profesión médica de Puerto Rico, a miembros de la colonia española y a los estudiantes de medicina por haber provisto fondos para que se erigiera esta estatua al doctor Koppisch. Citamos de su comunicación:

"Ni la dedicatoria que escribió el poeta, ni los discursos de develación de la estatua, nada de lo poco publicado, ha reflejado quienes han sido los que posibilitaron por su voluntad y por su generosidad, que esta magnífica escultura de Pablo Serrano perpetúe en figura uno de los ejemplares de nuestra actual clase médica. Enrique Koppisch ha pertenecido a la generación en que maduró en cuerpo vigoroso y digno la medicina de Puerto Rico. Ha sido uno de los exponentes más efectivos de nuestro actual progreso y prestigio. Esto lo conocían los médicos, y su respuesta al grupo de estudiantes que quería honorificar al Maestro lo ha proclamado elocuentemente.

"Desde San Juan a Ponce, desde Arecibo a Mayagüez, los médicos han acudido a la llamada en forma que ha colmado las esperanzas y las necesidades del Comité Organizador. De tal manera ha sido, que la gestión generalmente ardua de recoger fondos, en este caso, ha sido una gestión premiada con la alegría de recibir siempre respuestas positivas y generosas. En diferentes reuniones de facultad de hospitales en que se exponía el proyecto, el presidente de la facultad coreaba la exposición diciendo éstas o parecidas palabras: 'Además de lo que han oído ustedes, yo quiero añadir que durante un número de años, el Dr. Koppisch nos ha hecho las autopsias y la patología de este hospital sin cobrar nada. Ha habido un gesto que supone un reconocimiento y homenaje a la actual generación médica. Un grupo de selectos miembros de la colonia española ha concurrido con una aporta-

ción sustancial señalando que querían corresponder a la cordialidad con que la clase médica de Puerto Rico ha invitado y recibido a los destacados médicos españoles que nos han visitado en los pasados años. Lo hacían uniéndose a los médicos puertorriqueños en el homenaje al destacado compañero. Y así resulta que la clase médica de Puerto Rico ha sido cuerpo y puso vida al glorificar al excelso compañero, Dr. Enrique Koppisch. Honrar, honra".



ESTATUA: A la izquierda el Presidente de la Universidad de Puerto Rico, Lic. Jaime Benítez y la Sra. Cristina Soler Vda. de Koppisch; a la derecha, el Decano de la Escuela de Medicina, Dr. Adán Nigaglioni, y el Sr. Aníbal Marín, Presidente de la SAMA, observan la estatua erigida al Dr. Enrique Koppisch en los terrenos de la Escuela de Medicina.

CARDIOVASCULAR RESEARCH INVESTIGATORSHIP AWARDS

The Puerto Rico Heart Association and the American Heart Association, in conjunction with the University of Puerto Rico School of Medicine, announces a new program of Cardiovascular Research Investigatorship Awards.

These awards will enable U. S. citizens holding an M. D., Ph.D., or equivalent degree, to spend essentially full time conducting independent research in the broad field of cardiovascular disease and function in any department at the University of Puerto Rico School of Medicine in San Juan.

One award will be made each year and will consist of a stipend in excess of $10,000 per year for three years, plus an initial departmental grant of $2,000, fringe benefits, and a yearly stipend increment.

During the tenure of the award the Investigator will also hold a concurrent academic title in the University of Puerto Rico School of Medicine.

The deadline date for submission of applications is September 15, 1966, for awards beginning July 1967.

Inquiries for futher information and application forms should be sent to:

Chairman, Research Committee
Puerto Rico Heart Association
Box 8215, Fernández Juntos Station
Santurce, Puerto Rico 00910.

Nacionales

CONFERENCE OF OFFICERS OF STATE MEDICAL SOCIETIES

The Conference of Presidents and Other Officers of State Medical Societies, which will be held Sunday, June 26th, beginning at 9:30 A.M. at the Palmer House in Chicago.

The featured speakers for this program will be Dr. Angus Murray, President of the Australian Medical Association, who will relate the Australian doctors' story of defeating the government program to fully socialize the medical profession of Australia. The other speaker will be Mr. Richard M. Nixon, former Vice President of the United States. The President of the Conference is Dr. Walter C. Bornemier of Chicago.

CARDIOLOGY NINE MONTH TUTORIAL PROGRAM

A nine month tutorial program in Cardiology September 15, 1966 to June 15, 1967, will be offered by the Institute for Cardiopulmonary Diseases. Scripps Clinic and Research Foundation, La Jolla, California. This will be an intensive academic effort covering the field of cardiovascular diseases and is especially designed for the psysician. U. S. A. or abroad, who wants an intensive orientation in cardiology. The objective will be to offer training in the broad discipline of academic cardiology: the techniques of teaching, the use of the literature, the preparation of a manuscript, the art of consultation, history taking, the methods of the specialty (auscultation, x ray, fluoroscopy, electro and vectorcardiography, phonocardiography, cardiac catheterization, angiography, pulmonary function studies), the care and use of experimental animals, an introduction to biophysies and statistics, the selection and maintenance of equipment, maintenance of files and records. Tuition $1,000.

For information, write:
Executive Secretary, Institute for Cardio Pulmonary Diseases
Sscripps Clinic and Research Foundation
La Jolla, California
A formal program of the American College of Cardiology.

ANNUAL OTOLARYNGOLOGIC ASSEMBLY

October 1 through 7, 1966. *The Annual Otolaryngologic Assembly of 1966* will be held October 1 through 7, 1966, in the new Illinois Eye and Ear Infirmary at the Medical Center, Chicago. The Department of Otolaryngology of the College of Medicine of the University of Illinois offers a condensed postgraduate basic and clinical program for practicing otolaryngologists under the direction of Doctor Emanuel M. Skolnik. It is designed to bring to specialists current information in medical and surgical otorhinolaryngology.

Interested physicians should direct communications to the mailing address:

Department of Otolaryngology
P. O. Box 6998
Chicago, Illinois 60680

COURSE IN POSTGRADUATE GASTROENTEROLOGY

The Anual Course in Post graduate Gastroenterology of the American College of Gastroenterology will be given at the Bellevue Stratford in Philadelphia, Pa., 27, 28, 29 October 1966.

The Moderators for the Course will again be Dr. I. Snapper, Consultant, Ft. Hamilton Veterans Administration Hospital, Brooklyn, N. Y. and Dr. John L. Madden, Clinical Professor of Surgery, New York Medical College and Director of Surgery, St. Clare's Hospital, New York, N. Y.

The faculty for the Course will be drawn from the Medical Schools in and around Philadelphia. The subject matter to be covered, from the medical as well as the surgical viewpoint, will be essentially, the diagnosis and treatment of gastrointestinal diseases and comprehensive discussions of diseases of the esophagus, stomach, pancreas, liver and gallbladder, small intestine and colon. A session on instrument technics will be held at the Albert Einstein Medical Center, Northern Division.

For further information and enrollment, write to the American College of Gastroenterology, 33 West 60th Street, New York, N. Y. 10023.

EIGHTH NATIONAL CONFERENCE ON THE MEDICAL ASPECTS OF SPORTS

The Eighth National Conference on the Medical Aspects of Sports, sponsored by the American Medical Association under the auspices of its Committe on the Medical Aspects of Sports, will be held in Las Vegas, Nevada, at Caesar's Palace on November 27, 1966. The Conference is held annually in conjunction with and on the first day of the Clinical Convention of the American Medical Association.

As was true of the previous seven Conferences, the Eighth will cover a wide range of subjects of interest to those serving school and college athletic programs. Included will be forums and discussion sections relating to criteria for immediate management of knee injuries, resources for grass roots supervision of sports, medical preparations for international competitions, and the relationship of athletic fitness to physical fitness. Among the

speakers will be Merritt Stiles, M. D., 2d Vice President of the U. S. Olympic Committee, and Donald O'Donoghue, M. D., President of the American Academy of Orthopedic Surgeons. Robert S. Rocke, M. D., Medical Examiner for the California State Athletic Commission, will address the Conference Luncheon.

The Conference is open to key nonmedical athletic personnel as well as interested physicians. Those who would like to receive further information concerning the Conference should address the Secretary, Committee on the Medical Aspects of Sports, American Medical Association, 535 North Dearborn Street, Chicago, Illinois 60610.

Internacionales

CUARTA CONVENCION NACIONAL DE PEDIATRIA (SANTO DOMINGO)

La Cuarta Convención Nacional de Pediatría ha sido fijada para los días 5, 6 y 7 de agosto próximo.

Los temas básicos serán:

1. Enfermedades a virus
2. Diarrea epidémica
3. Trastornos convulsivos.

Asistirán como invitados especiales los profesores Dr. Alfredo Heredia D., Jefe del Servicio de Infecciosos del Hospital de Niños de México y Dr. Luis P. Sánchez Longo, titular de la cátedra de Neurología de la Universidad de Puerto Rico.

Los interesados pueden dirigirse a la Sociedad Dominicana de Pediatría, Ap. postal 357, Santo Domingo, República Dominicana, y recibirán detalles completos a vuelta de correo.

AMERICAN MEDICAL SOCIETY OF VIENNA

POST-GRADUATE COURSES OFFERED IN VIENNA

A new diversified program of postgraduate seminars in all medical specialties and subspecialties has been announced by the American Medical Society of Vienna.

Top medical scientists of the University of Vienna Clinics will direct practical sessions, surgical operations, round table discussions, and grand rounds; teaching lectures are not usually given. Arrangements can be made on an individual basis or for groups through the office of the Society and the time spent at these seminars, a few days or weeks, or extended courses lasting three and ten months, can be tailored to the individual. A Medical Congress Letter is given at the end of the short sessions and a diploma is awarded by the Medical Faculty of the University of Vienna upon completion of the longer seminars.

These courses represent bona fide medical continuation training, and expenses incurred in connection with these seminars are deductible, according to the IRS ruling. The subjects especially favored by American doctors studying in Vienna are: Surgery and its subspecialties; Gynecology; Ophthalmology; Ear, Nose and Throat; Urology; and Dermatology.

The club headquarters of the Society are located in the University section of Vienna and are close to the University Clinics. Every possible amenity is provided to the visiting doctor. The club rooms and the extensive library of the Society have become a study center for English-speaking doctors in Europe. Hotel accommodations in Viena are available in all class prices.

Further information may be obtained by writing to Dr. M. A. Kline, Executive Secretary of the American Medical Society of Vienna, Universitatsstrasse 11, Vienna I, Austria.

The American Medical Society of Vienna has a long and distinguished history. Since its founding in 1879, tens of thousands of English-speaking doctors have been aided to attend seminars arranged in cooperation with the world famous medical faculty of the University of Vienna. Besides this primary activity of the organization, it provides help and assistance to the medical students of English-speaking countries abroad and administers examinations required by foreign medical graduates to enter the United States as set up by the Educational Council of Foreign Medical Graduates. Furthermore, a fund organized by the American

Medical Society of Vienna in conjunction with the World Health Organization provides financial aid for medical students and graduates of developing countries studying in Vienna.

XVI REUNION NACIONAL DE LA SOCIEDAD MEXICANA DE OTORRINOLARINGOLOGIA

La XVI reunión nacional de la Sociedad Mexicana de Otorrinolaringología se efectuará en la ciudad de Guadalajara, Jal., del 1ro. al 5 de mayo de 1966. La organización está a cargo del Dr. Federico Reinking, Jr., Presidente, y del Dr. Juan Oberhauser, Secretario.

Para cualquier información puede dirigirse a Doctor Mora 9-10, México 1, D. F. o llamar a los teléfonos 12-31-01 y 12-45-85.

Agosto 20-25, 1966. *Noveno Congreso Internacional de Enfermedades del Tórax.*

PAN PACIFIC SURGICAL ASSOCIATION TENTH CONGRESS

The Board of Trustees of the Pan-Pacific Surgical Association announces the dates of the Tenth Congress in Honolulu and the Second Mobile Educational Seminars which travels to countries bordering the Pacific basin.

Part I, the Honolulu portion of the Congress, will convene at the Princess Kaiulani Hotel on September 20, 1966, and continue through September 28.

Part II and III will depart Hawaii on September 28 and travel to Japan and Hong Kong with Part II returning to San Francisco on October 10, in time for the opening of the American College of Surgeons, and Part III continuing on to the Philippines, Thailand, India, Singapore, Australia and New Zealand, returning to Hawaii on November 1, 1966.

The Tenth Congress offers an extensive scientific program presented by more than 450 leading surgeons from the United States and 22 other countries in 12 different specialties: Colon and Anorectal Surgery, General Surgery, Neurosurgery, Obstetrics and Gynecology, Ophtalmology, Otolaryngology, Orthopedics, Plastic Surgery, Thoracic-Cardiovascular Surgery, Urology, Anesthesiology and Radiology. All physicians and surgeons are invited to attend these meetings.

In this space age, diseases are no longer confined to geographical boundaries and it has become essential for the medical profession everywhere, to share its scientific knowledge and efforts.

Therefore, Pan-Pacific with its Mobile Seminars, is expanding its activities in teaching, education and dissemination of knowledge to doctors living in the Pacific rim countries who are unable to participate in the Honolulu portion of the Scientific Congresses, in exchange for further education and skill in the diseases unique to the Pacific areas. The Pan-Pacific Surgical Association believes, through the vehicle or medium of medicine and surgery, that our greatest contribution to peace and harmony among all men of all nations can be realized.

For further information, please write: Pan-Pacific Surgical Association, Room 236, Alexander Young Building, Honolulu, Hawaii 96813.

Oct. 23-29, 1966 IX International Cancer Congress, Tokyo, Japan. A charter flight and several group flights are contemplated, thus substantially reducing the cost of transportation. Members of the immediate family of congress participants will be eligible. Anyone interested should communicate with Tirsch Marks, M.D., 435 East 57th Street, New York 22, N. Y.

Instrucciones para los Autores:

El Boletín acepta para su publicación artículos relativos a medicina y cirugía y las ciencias afines. Igualmente acepta artículos especiales y correspondencia que pudiera ser de interés general para la profesión médica.

El artículo, si se aceptara, será con la condición de que se publicará únicamente en esta revista.

Para facilitar la labór de revisión de la Junta Editora y del impresor, se requiere de los autores que sigan las siguientes instrucciones:

a) Los trabajos deberán estar escritos a máquina a doble espacio y por un solo lado de cada página, en duplicado y con amplio margen.

b) En página separada debe incluirse lo siguiente: título (no excediendo de 80 letras y espacios), nombre del autor (es), institución y dirección postal del autor.

c) Artículos referentes a resultados de estudios clínicos o investigaciones de laboratorio deben organizarse bajo los siguientes encabezamientos: (1) introducción, (2) material y métodos, (3) resultados, (4) discusión, (5) resumen (en español e inglés), y (6) referencias.

d) Artículos referentes a estudios de casos aislados deben organizarse en la siguiente forma: (1) introducción, (2) observaciones del caso, (3) discusión, (4) resumen (en español e inglés), (5) referencias.

e) Las tablas, notas al calce y leyendas deben aparecer en hojas separadas.

f) Si un artículo ha sido leído en alguna reunión o congreso, así debe hacerse constar como una nota al calce.

g) Deben usarse los nombres genéricos de los medicamentos. Podrán usarse también los nombres comerciales, entre paréntesis, si así se desea.

h) Se usará con preferencia el sistema métrico de pesos y medidas.

i) Las fotografías y microfotografías se someterán como copias en papel de lustre sin montar. Los dibujos y gráficas deben prepararse a tinta negra y en papel blanco. Todas las ilustraciones deben estar numeradas (números arábigos) e indicar la parte superior de las mismas. Debe escribirse una leyenda para cada ilustración.

j) Las referencias deben ser numeradas sucesivamente de acuerdo con su aparición en el texto. Los siguientes ejemplos pueden servir de modelo:

6. *Koppisch, E.* Pathology of arteriosclerosis. Bol. Asoc. Med. P. Rico 46: 505, 1954. (artículo de revista).
4. *Wintrobe, M. M.* Clinical Hematology, 3rd Ed. Lea and Febiger, Philadelphia, 1952, p. 67. (libro).

Deben usarse solamente las abreviaturas indicadas en el Cumulative Index Medicus que publica la Asociación Médica Americana.

Instructions to Authors:

The Boletín will accept for publication contributions relating to the various areas of medicine surgery and allied medical sciences. Special articles and correspondence on subjects of general interest to physicians will also be accepted. All material is accepted with the understanding that it is to be published solely in this journal.

In order to facilitate review of the article by the Editorial Board and the work of the printer, the authors must conform with the following instructions:

a) The entire manuscript, including legends and references, should be typewritten double-spaced in duplicate with ample margins.

b) A separate title page should include the following: title (not to exceed 80 characters and spaces), author's name (s); institution, and author's mailing address.

c) Articles reporting the results of clinical studies or laboratory investigation should be

organized under the following headings: (1) introduction, (2) material and methods, (3) results, (4) discussion, (5) summary in English and Spanish, (6) references.

d) Case reports will include (1) introduction, (2) description of the case, (3) discussion, (4) summary in English and Spanish, (5) references.

e) Tables, footnotes and legends to figures should appear in separate sheets.

f) If the paper has been presented at a meeting, the place and date should be stated as a footnote.

g) Generic names of drugs should be used. Trade names may also be given in parenthesis, if desired.

h) Metric units of measurement should be used preferentially.

i) Photographs and photomicrographs should be submitted as glossy prints, unmounted. Drawings and graphs should be made in black ink on white paper. All illustrations should be numbered (Arabic) and the top indicated. A legend should be given for each.

j) References should be numbered serially as they appear in the text. The following form will be used:

6. *Koppisch, E.* Pathology of arteriosclerosis. Bol. Asoc. Med. P. Rico 46: 505, 1954. (for journal articles).
4. *Wintrobe, M. M.* Clinical Hematology, 3rd Ed. Lea and Febiger, Philadelphia, 1952, p. 67, (for books).

Abreviations will conform to those used in the Cumulative Index Medicus, published by the American Medical Association.



PHOTO BY CHADWICK HALL USING A FISH-EYE LENS

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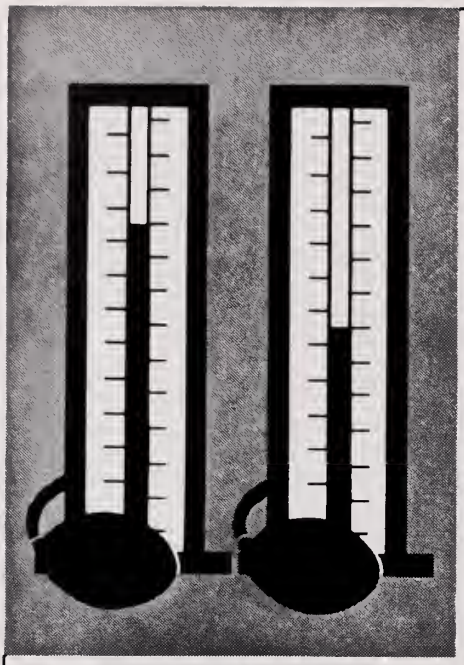
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SOCIACION MEDICA DE PUERTO RICO

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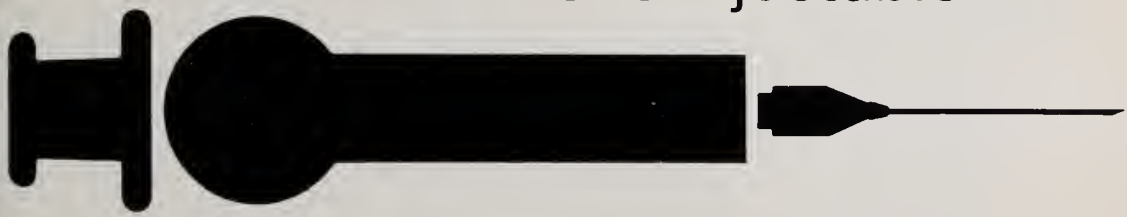
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PHYSICAL MEDICINE IN ACTIVE RHEUMATOID ARTHRITIS

Leonard F. Bender, M.D., M.S.

Physical medicine is used in the treatment of active rheumatoid arthritis to attain two major objectives: preservation of joint function and relief of symptoms. A third objective, improved functional capacity, becomes more important as the disease becomes less active.

Physical and other therapeutic measures which have been used in the management of rheumatoid arthritis fall roughly into two categories, those of proved value and those of only *doubtful value* (1). The doubtful measures include massive doses of vitamins, special diets, injections of bee venom, and others. The measures of proved value include general body rest, rest of the acutely involved joints, physical therapy, occupational therapy, well — balanced diet, salicylates, an even climate, orthopedic measures, gold injections, removal of focal infections, x-ray therapy, and steroids. A few measures stand out as being of special importance. These are rest, rest of affected joints, routine use of salicylates, and physical measures. Rest does not mean the patient's confinement to bed, but rather a judicious balance of activity and general body rest. Rest of the acutely involved joints is possible without significant stiffening, if one gauges the amount of activity permitted against the amount of aggravation and pain caused by that activity. At our hospital, salicylates remain the most consistently useful and least harmful of the drugs used to combat rheumatoid arthritis. Our usual regimen for physical therapy combines heat, massage, and exercise with bracing.

Heat is used prior to therapeutic exercise for its physiologic effects as an analgesic and antispasmodic agent. By making the joints and muscles around them less painful and more relaxed, the heat serves a useful therapeutic function and enables the patient to perform therapeutic exercises more effectively.

Many sources of heat are available; the simpler ones are preferred. Since most patients must combat the deforming effects of rheumatoid arthritis themselves, it is our purpose as physicians to outline an effective program that the patient can carry out at home. Infrared and hydrotherapy, including Hubbard tank, whirlpool, and contrast baths, paraffin baths and hydrocollator

From the Department of Physical Medicine and Rehabilitation, The University of Michigan, Ann Arbor, Michigan.

Presented at the First Caribbean Congress of Physical Medicine and Rehabilitation, San Juan, Puerto Rico, April 29, 1966

packs, are all forms of heat therapy which can be obtained or simulated at home. The Hubbard tank is used to provide heat and buoyant support when multiple joints in different extremities are involved. If the physician desires the additional effect of a mild fever therapy, the water temperature can be adjusted so that the patient's body temperature becomes elevated to 101° orally during the course of a 20-30 minute immersion. A most-air cabinet will provide the same heating effects but no buoyant support of the extremities. The whirlpool bath is used to give hydrotherapy to one arm, one leg, or possibly both legs. Contrast baths and paraffin baths are used primarily for the hands and wrists; the paraffin, preferred by most patients, leaves the skin warm, supple, and lubricated for massage and exercise. Infrared lamps may be used singly, at a distance that provides comfortable warmth to one or two major joints, or they may be combined in the form of an infrared baker to cover half or all of the joints of the body simultaneously. Hydrocollator packs can be applied to one or more joints simultaneously; they have the advantage of being very low in cost initially and being reusable almost indefinitely. They are a form of heat that is less likely to cause burns.

Short — wave and microwave diathermy, diapulse, and ultrasound are rarely if ever used or recommended for the treatment of rheumatoid arthritis. They are all excellent sources of penetrating energy which produces deep heat, but their application is limited to one or two joints at a time and it would be impractical if not impossible for a patient to continue similar treatments at home.

Massage is no longer very highly regarded in the management of rheumatoid arthritis. A combination of stroking and kneading movements does stimulate the flow of lymph from an extremity toward the thoracic duct (2), and in cases where lymphedema is present, massage would be beneficial. Also in those patients where the muscles around an involved joint are tense and painful, massage may have a relaxing effect. We never prescribe general body massage since this is too time-consuming and tiring to the patient.

Therapeutic exercise is the most important physical agent used in the treatment of rheumatoid arthritis. In the early stages, exercise is used to prevent or minimize joint deformity. This is accomplished by use of proper body-positioning, range-of-motion exercises, and selective muscle-strengthening.

In order to prevent or minimize joint deformities by proper positioning, it is necessary to anticipate deformity. Certain types of deformity are quite common; others are most unusual. In the arm, the common deformities are shoulder adduction, elbow flexion, wrist flexion and pronation, flexion, ulnar deviation, and volar subluxation of the proximal phalanx on the metacarpal; and flexion of the proximal and distal interphalangeal joints. In the legs one commonly sees flexion and adduction of the hips, flexion and valgus deformity of the knees, lateral deviation and volar subluxation of the phalanges on the metatarsals, and occasionally posterior subluxation of the tibia. It is interesting to note that these joint deformities are similar in many respects to those seen in hemiplegia and Parkinson's disease, except that

the rheumatoid deformity is more severe. By anticipating these deformities one can minimize the damage by instructing the patient to rest his joints in a position other than the common position of deformity. Thus the shoulder should be rested with the elbow held away from the side of the body, and the fingers should be positioned so that they are in radial deviation with the phalanges well supported at the MCP joint. It is often desirable to assist positioning of the hands by means of plastic or metal braces and splints. A plastic wrist cock-up splint has been designed at the University of Michigan which straps on the volar surface of the forearm, holds the wrist in a neutral or slightly dorsiflexed position, and supports the proximal phalanx, while putting a downward shear force on the metacarpal heads by means of a Velcro strap which extends either to the distal end of the proximal phalanx or to the fingertips, depending on the physician's prescription (Figure 1). These are used primarily at night, but patients are also encouraged to wear them in the daytime.



Fig. 1: Plastic cock-up splint for the wrist.

Range-of-motion exercises are designed primarily to maintain or improve joint range of motion. At the stage of early involvement, it is important that the joints be taken through their full range of motion at least once daily to maintain that range. This can be done actively by the patient or with the assistance of a therapist, or it may be done passively by the therapist alone. I would like to stress two points in regard to this type of exercise, however: first, it should be limited to those joints which are actively involved by the disease process at the moment. It has been our experience that patients who are instructed to exercise all or most of their joints daily do not exercise any of them. It is most important to have the patient exercise those joints which are involved and to be sure that he does do it daily. A second important consideration, again, is the matter of common deformities. It is foolish to exercise a joint toward the position of common deformity, just as it is not sensible to position joints in that way. Therefore it seems useless, if not frankly detrimental, to stress full range of motion of the metacarpophalangeal joints including ulnar deviation and flexion. Instead, the patient should be instructed specifically to exercise his fingers toward the radial deviated position.

Closely interwoven with range of motion exercises are the selective strengthening exercises. By this I mean that muscles which will help to prevent the common deformities should be strengthened. Thus the radial deviators of the fingers and the extensors of the wrist and fingers should be strengthened, as well as the extensors, abductors, and rotators of the shoulder. In



Fig. 2: Fifth finger adduction splint with spring wire to reduce ulnar deviation of the fingers and permit all normal motions in MCP and IP joints.

joints which are acutely inflamed, repetitious motion may also be harmful and strengthening should be accomplished through brief, maximal exercise and isometric exercise techniques.

Once deformity has become established to any extent, it will be necessary to reduce that deformity in addition to following the tenents of therapy already outlined. The reduction of an established deformity is best accomplished through gentle, passive stretching which can be accomplished either through exercise or by orthetic devices. A simple metal splint to reduce ulnar deviation and increase stability at the fifth MCP joint has been designed (3) (Figure 2) The patient is able to wear this splint during all normal activities. It permits normal flexion and extension but reduces ulnar deviation to a minimum. In this way the fifth digit acts as a support against the fourth, and so on across the hand.

Finally, in cases where the disease has regressed and yet the joints cannot resume normal position or functioning, it becomes necessary to increase the patient's functional capacity through adaptive equipment, assistive devices, and alteration of his environment. Assistive devices should enable him to perform daily activities by himself, and perhaps even to pursue a vocation.

Summary

Physical medicine in active rheumatoid arthritis consists of the judicious use of preliminary heat, massage, and therapeutic exercise. The therapeutic exercise is designed to minimize the risk of joint deformity, or reduce deformity that is already established. Through assistive devices, braces,

and splints, proper joint alignment can be maintained and the patient's range of activities increased.

Resumen

Para resumir, en la artritis reumatoidea activa la Medicina Física interviene, inicialmente, mediante el uso adecuado de calor local, masajes y ejercicios, para disminuir el riesgo de la deformación articular, o para reducir la deformidad ya existente; por medio de soportes y otros artefactos mecánicos adecuados, secundariamente interviene para mantener el alineamiento articular que permita la mayor mobilidad posible a las actividades del paciente.

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SURGICAL TREATMENT IN ACTIVE RHEUMATOID ARTHRITIS

E. D. Henderson, M.D.

As almost all physicians know, the treatment of rheumatoid arthritis is a very complex, time-consuming, at times exasperating, and always an uncertain affair. The so-called classical, conservative treatment of rheumatoid arthritis is being very adequately discussed in this symposium and I will not dwell on it here.

I hope to be able to make a case for the cooperation of the surgeon and the internist in treating rheumatoid arthritis. I will attempt to show that, in many cases, a surgical approach to the problem may, in fact, be more conservative than prolonged treatment with braces, splinting, stretching, and other physical means of attempting to preserve joint function or maintenance of the joint in a functional position. Unfortunately, orthopedic surgeons and physicians of internal medicine seldom approach the problem of rheumatoid arthritis in consort. All too frequently they are suspicious of each other's motives and methods and have not learned a common language with which they can communicate. It is my purpose, here, to attempt to indicate where, in our experience, various surgical procedures may be of help, not only in correcting deformities of burned out rheumatoid arthritis, but also to aid in the active treatment of patients in whom the disease is still either very active or smoldering.

We should all agree at the outset that the primary responsibility for the treatment of a patient with active rheumatoid arthritis rests with the internist who is particularly interested in this disease. The medical regime instituted by him when closely followed, evaluated and changed as the disease progresses or subsides, is obviously of paramount importance to the patient. What does he do, however, when one or more joints refuses to respond to such a regime? For instance, the patient who is doing well in all respects except for continued significant synovitis in the knees with pain, muscle spasm and limitation of motion and gradual erosion of the articular surfaces, the subsequent relaxation of the ligaments, instability of the joints and severe mechanical pain. The question really is whether something can be done for these individual joints which are not responding satisfactorily to a medical regime before they reach the stage of severe mechanical disability.

Presented at the First Caribbean Congress on Physical Medicine and Rehabilitation San Juan, Puerto Rico, April 25-29, 1966.

From the Orthopedic Surgical Service, The Mayo Clinic, Rochester, Minnesota.

In the year 1900, a French surgeon named Mignon discussed the results of synovectomy, both for tuberculosis and for rheumatoid arthritis. In the 1920's, Allison and Coonse, Jones, Steindler, et al advocated synovectomy in rheumatoid joints and, in the orthopedic literature, reports of results of synovectomies of various joints have been appearing in increasing numbers. In the past few years, surgical synovectomies of the knees, wrists, metacarpophalangeal joints and interphalangeal joints of the fingers have been done in greatly increased numbers. Probably the reason for choosing these joints is that, technically, it is easier to do a synovectomy and debridement of the joint in these areas than in other more complex and less easily accessible joints, such as hips, elbows, shoulders, etc. For example, in 1965, Ramsey and Londonberry reported their results in synovectomies of 103 joints, 52 of which were knee joints, 15 wrist joints, 14 metacarpophalangeal joints and 9 interphalangeal joints. They had also done them in lesser numbers in hips, ankles, shoulders and elbows. It is significant that they, as well as almost all other surgeons, report much better clinical results when the synovectomies are done rather early in the disease, when there is synovitis but very little objective evidence of mechanical destruction of the joint. On the other hand, even in joints which have mechanical destruction, and where there is a great deal of stiffness, they reported 29 out of 34 in which pain had been almost completely relieved. Following the synovectomy, a new synovial lining is formed and this lining is capable of dialysis of synovial fluid. Technic is important in these procedures and it is extremely important to minimize the inflamatory reaction as much as possible prior to surgery by adequate rest of the involved joint and, in the especially florid cases, perhaps to minimize the inflammatory reaction by injection of steroids. The operative technic should be meticulous with good hemostasis before closure of the wound. Posteoperatively, these patients should begin motion early and every attempt made to obtain a good range of motion, particularly in the range that is functional. Meticulous attention to muscle reeducation, coordination, and strengthening is extremely important.

As far as I can determine, there is no evidence that such operative procedure produce exacerbations or flare-ups of the arthritis. Objective reporting of the results of surgical treatment is extremely difficult so far as assessing the permanent benefit to be derived from each surgical procedure. All we can do is to report to you on a number of surgical procedures in various parts of the body which, in our clinical judgment, appeared to benefit the patient in a large enough percentage of cases to be worthwile of consideration. The fact that these surgical procedures are being done in increasing numbers in France, Britain and the United States would indicate that at least the surgeons are convinced that these operations do give lasting benefit to the patient.

I would, therefore, like to call to your attention what appears to be the consensus at the present time of the value of certain operative procedures which can be done in the active phase of rheumatoid arthritis. This is probably best presented on a regional basis, rather than grouped together by various operative procedures. In some cases, we have done so many operations on an individual patient that it is almost embar-

rassing to report it. None the less, each operative procedure has, in the opinion of the surgeon and the patient, been of benefit and the patient has been not only willing to have the next operation, but in many cases has asked for it.

Spine

Osteotomies of the spine should be mentioned in passing, although they are seldom done in the active phase of rheumatoid spondylitis. The osteotomies are done to correct severe deformities of the rheumatoid spondylitic, which are so severely disabling that the patient cannot see far enough in front of him to function in even a reasonable fashion. These osteotomies are usually done either in the lumbar or the cervical spine and must be considered hazardous procedures because of the danger to the spinal cord and the spinal nerve roots, either from bony impingement or hemorrhage.

The condition of atlanto-axial subluxation due to relaxation of the ligaments between the first and second cervical vertebrae is one which is not recognized as often as it should be. This condition is frequently present in rheumatoid arthritis which involves the peripheral joints in contrast to the rheumatoid spondylitic in which the usual outcome is a rigid spine. Subluxation of the first on the second cervical vertebrae should be suspected when the patient complains of occipital headaches when in the upright position or when sitting in a stooped-over position for a long period of time. Flexion extension views of the upper cervical spine will show an abnormal mobility between the first and second cervical vertebrae. In these cases, we have been able to eliminate the symptoms and stabilize the cervical spine by wiring the spinous processes and laminae of the first, second and third cervical vertebrae together and applying iliac bone grafts to effect a fusion in this area. If the wiring is done with a heavy gauge steel wire and securely fixed, practically no postoperative immobilization is necessary and successful fusions have been obtained in over 90 per cent of the cases. This operation should be considered at any time in the course of rheumatoid arthritis when the symptoms and positive physical findings indicate such an instability.

Shoulder

Many of the classical orthopedic operations on the shoulder are not applicable to rheumatoid arthritis. For instance, an arthrodesis is almost never advisable because of the stiffness of other joints of the upper extremity and of the spine. In my own personal experience, I have done synovectomies of the shoulder joint on three occasions, in each case because of huge rheumatoid synovial cysts which were causing the patient severe pain and limitation of motion. After synovectomy, the patients did not have any better function of the shoulder from a mechanical standpoint but, in all three, the pain has been relieved. This is also true in the case reported by Wilkinson and Lowry.

Elbow

Synovectomy of the elbow has not, to my knowledge, been performed many times in this country. Wilkinson and Lowdy, in their paper, report the results of seven cases in which pain was relieved in five and not relieved in two. In addition, one of the elbows lost a significant degree of function following the synovectomy. In advanced stages of rheumatoid arthritis of the elbow joint, there is not only roughness of the articular surface, but a good deal of bone destruction. It would seem logical to consider doing resections of the elbow joint with or without interposition of some type of membrane such as fascia or teflon in cases in which there are severe pain, instability and weakness. One of my colleagues, Dr. L. F. A. Peterson, has designed an olecranon prosthesis which he has used in one patient with quite a satisfactory result. This is an area in which surgery is in its infancy.

Forearm

I have seen one case, operated by Doctor Clayton of Denver, in which the head of the radius and the distal end of the ulna were resected simultaneously because the patient had severely painful

and limited forearm rotation. The result of this surgery was quite satisfactory. It would seem that resection of the head of the radius would be a logical procedure in cases in which forearm rotation was severely limited and painful because of arthritis in the radiohumeral joint.

Wrist

It has often been stated, particularly among hand surgeons, that the wrist is the key to the function of the hand. Since World War II, when hand surgery has become an ever expanding branch of the surgical art, the interest of surgeons in the wrist affected by rheumatoid arthritis has been increasing rapidly. We have all seen patients in which the hands were terribly deformed, but in which an amazing degree of function remained because the patient had good wrist function. In the late forties and early fifties, surgery on the wrist was done primarily to correct long-standing deformities of the wrist in burned out rheumatoid arthritis. Such procedures as arthrodesis, resection of the proximal row of carpal bones, osteotomies of the radius, and resection of the distal ulna were performed to try to re-establish the wrist in a functional position, that is from neutral to 45 degrees of dorsiflexion, to give the hand an opportunity to have some mechanical stability. However, in the last fifteen years, indications for surgery on the wrist have advanced to include synovectomies of the wrist joint, itself, and the flexor and extensor tendon sheaths in the active phases of the disease. In some cases, the synovitis of the flexor tendon sheaths may be the earliest symptom of rheumatoid arthritis. Clayton, in his series, reported two patients in which a so-called nonspecific tenosynovitis of the flexor tendon sheaths was the earliest symptom of a subsequent occurring rheumatoid arthritis. Compression of the median nerve by the rheumatoid tenosynovitis in the carpal canal is a rather common cause of so-called carpal tunnel syndrome. Many times, the symptoms of pain paresthesias in the fingers and hand are masked by other evidence of rheumatoid arthritis and the physician examining the patient does not realize that the patient is having severe compression of the median nerve beneath the transverse carpal ligament. Relief of these symptoms is quite easy by sectioning the transverse carpal ligament surgically. At the same time, it seems wise to do a synovectomy of the flexor tendon sheaths in the carpal canal in the distal forearm. Relief of symptoms is usually prompt, at least insofar as the pain and paresthesias due to the median nerve compression is concerned. Furthermore, with surgical synovectomy of the flexor tendon sheaths, relief of symptoms appears to be permanent.. This, of course, does not relieve the symptoms of flexor tendon sheath tenosynovitis in the distal palm of the hand and the fingers and it is possible that there will be synovitis of these tendons, as well.

On the dorsal surface of the wrist, rheumatoid tenosynovitis may be an early manifestation of rheumatoid disease and sometimes is diagnosed initially as a ganglion. Synovitis begins beneath the dorsal carpal ligament and extends distally, producing swelling distal to the edge of the ligament. At the same time, there may be active synovitis of the wrist joint, itself, and of the distal radial ulnar joint. It is in this situation that rheumatoid nodules frequently involve the tendons and invade them so that weakness occurs and rupture of the extensor pollicis longus or any of the common finger extensors may occur. This may be aggravated by dorsal dislocation of the distal end of the ulna and roughness of this bone, but most surgeons now feel that the primary disease is invasion of the tendons by rheumatoid nodules. If this condition does not subside with splinting and injections and other forms of conservative treatment, surgery is indicated early to prevent tendon damage. It is usually wise to do a synovectomy of the extensor tendon sheath and of the wrist joint, itself, if it is involved. Occasionally the wrist is so unstable that resection of the distal ulna along with synovectomy of the wrist will produce ulnar subluxation of the wrist. In this case, the wrist should be fixed in a normal position with Kirschner wires for three to four weeks postoperatively.

In cases in which extensor tendons have ruptured, which they almost always do at the wrist joint level, surgical treatment is definitely indicated. The tendon function may be restored by a tendon graft, by side-to-side suture to other tendons which have not ruptured or by a tendon transfer using

the extensor indicis proprius or one of the wrist extensors as power. I am, personally, a little prejudiced in favor of tendon grafts, having done these in four cases with quite satisfactory long-term results. In this regard, it is important to point out that the intrinsic muscles extend the distal two joints of the fingers, so that with rupture of an extensor tendon, the metacarpophalangeal joint may be incapable of full extension, but the proximal and distal interphalangeal joints may be extended. This, superficially, looks like the usual type of deformity in the finger with arthritis involving the metacarpophalangeal joint with a flexion deformity and ulnar deviation. It is important, when examining such hands, to observe and palpate the common extensor tendons when the patient extends, or attempts to extend, the fingers. This makes the differential diagnosis easy.

Hand

The surgical treatment of the hand affected by rheumatoid arthritis has been effectively and repeatedly explained by a large number of surgeons interested in hand surgery throughout the world. Probably most physicians are well acquainted with the surgery to correct the ulnar drift of the fingers, the intrinsic contractures, the unstable interphalangeal and metacarpophalangeal joints, trigger fingers and many other manifestations of tenosynovitis including rupture of both flexor and extensor tendons. It seems reasonable to apply the principles of surgical intervention in the form of relatively early synovectomies of finger and thumb joints to the hand as well as the knees and other areas of the body. These excisions can be profitably combined with intrinsic muscle releases, repositioning of the extensor hood, resection of a portion of the metacarpal heads, arthrodeses of hopelessly deformed joints and selected tendon transfers in more advanced, but still active arthritis of the hands.

Hips

Although a few synovectomies of the hip joint have been done, there is no large series reported which would indicate that this is a successful operation as far as giving long-lasting relief of symptoms or of delaying the destructive changes in the articular surface of the joint. If there is any clinical or x-ray evidence of mechanical damage to the hip joints, the most logical surgical approach to the problem appears to be some sort of arthoplasty. There are advocates of the mold, or cup, arthroplasty and those favoring the metallic prosthesis. Both of these aim to eliminate or reduce pain and to preserve a reasonable range of motion in a useful arc, while still preserving stability. Arthrodesis of the hip is out of the question in most patients with rheumatoid arthritis because of the involvement of adjacent joints. The only other alternative is some sort of resection of the hip joint which provides adequate painless motion, but sacrifices mechanical stability.

Knees

As I have already indicated, the knee joint has been the subjet of considerable attention from the surgeons for a long period of time. It is easy to approach surgically. It is easy to evaluate as far as swelling, motion, tenderness, stability and surrounding muscle spasm is concerned. Usually the chief site of the synovitis is the anterior compartment of the joint. However, it is not at all unusual for the disease to present itself primarily as a popliteal cyst. Currently, it is the practice to do the synovectomy anteriorly if this seems the principle area of the synovitis, posteriorly if the reverse is true, and both anteriorly and posteriorly if the disease involves both compartments equally. The results of these operations indicate that in 70 to 75 per cent of the cases, prolonged relief of the subjective and objective signs of the synovitis can be expected. This included definite delay in the destructive effects of the rheumatoid arthritis on the joint surfaces. It the result is satisfactory in the first year postoperatively, it can be expected to last for more than 10 years. In our experience, we have seen good results to be evident for more than 20 years.

Ankle

The only surgical procedure which can control the pain and instability of the affected ankle joint

is an arthrodesis. This may be necessary in the advanced destructive phase, but is much more acceptable if the joints of the foot are mobile. An anterior synovectomy of the joint has been reported by Ramsey and Londonberry with indications that it is a satisfactory procedure. We have not had any experience with it.

Foot

There are two quite satisfactory operations available to control pain in the foot. The first is arthrodesis of one or more mid tarsal joints, particularly when these joints are involved without simultaneous involvement of the ankle or metatarsophalangeal joints. A triple arthrodesis, as described by Ryerson, may make the difference as to whether the patient can walk. Frequently, the metatorsophalangeal joints are so painful and deformed that walking is almost impossible and wearing of shoes is impossible. It has been long recognized that the toes are not essential to walking in modern society. Therefore, a surgical procedure which eliminates the joints without regard to the stability of the joints and, at the same time, removes the painful metatarsal heads has proved most effective in reducing pain and, at the same time, restoring the foot to a contour which will fit into a shoe. Resection of both the heads of the metartarsals and the bases of the proximal phalanges has, in our experience, almost invariably resulted in the patient being able to fit his foot into a shoe and greatly increased the range of his walking ability. In many instances, it is possible to preserve the head of the first metatarsal and do a Keller operation on the great toe if there is sufficient subcutaneous padding beneath this bone. If not, a resection of the first metatarsal head is perfectly acceptable. Obviously, these people do not have normal feet, but the improvement is evident to them as well as the surgeon.

I have tried to indicate that, in some instances in the care of the patient with rheumatoid arthritis, it is more conservative to consider some operative procedures to combat advancing disability and deformity than to continue with the more traditional forms of rest, splinting, stretching and exercises, which have so long been considered conservative therapy.

EL ENFERMO DE LEPRA AMPUTADO

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La deformidad del pie en el enfermo de lepra ocupa un lugar de primera importancia en su incapacidad física y ella, así como las amputaciones que origina, han sido motivo de especial interés por los autores quienes en el presente trabajo intentan hacer una exposición preliminar sobre este problema. Dada su complejidad nos referiremos exclusivamente al aspecto físico, dejando a un lado los aspectos psicológicos, sociales y vocacionales a pesar de que ellos son de un extraordinario interés e importancia dentro del proceso integral de rehabilitación. (*)

La lepra ataca fundamentalmente la piel, los nervios periféricos y algunos órganos de alta especialización funcional ocasionando incapacidad física fundamentalmente en manos, pies y cara. El ataque nervioso es troncular y terminal determinando parálisis motoras.y trastornos de sensibilidad que por su componente terminal tipifican y le confieren particular gravedad.

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(*) *Tampoco nos referimos a amputaciones en miembro superior que, aún cuando teóricamente posible, no se han practicado en Venezuela.*

En manos, a la deformidad paralítica de naturaleza troncular se agrega extenso compromiso sensorial que es factor determinante en el desarrollo de las graves mutilaciones. Por otra parte las intercurrencias agudas reaccionales originan severas deformidades fijas.

En pies, encontramos el mismo ataque motor y sensorial primario sobre el cual se injerta el problema de la úlcera plantar cuyo desarrollo incontrolado va a determinar en última instancia la amputación.

En cara, la incapacidad cae fundamentalmente en el terreno estético excepto en lo que se refiere al compromiso de la visión.

La úlcera plantar, por tanto tiempo una incógnita en su mecanismo de producción, sabemos hoy está ligada íntimamente a la dinámica desarrollada en un pie kinético con parálisis de su musculatura intrínseca y trastornos de la sensibilidad plantar. Es pues una expresión inespecífica de sufrimiento tisular traumático durante la marcha, cuya cicatrización es fácil al suprimir el factor determinante mediante el reposo. Es en la prevención de la recaída en donde radica la dificultad en el manejo de este problema.

Cuando la úlcera plantar no es controlada, se inicia un círculo vicioso con des-

trución de estructuras profundas (hueso-articulaciones) por infección secundaria, lo cual agrava la deformidad y desarrolla nuevas ulceraciones. De esta forma se compromete cada vez más la función del miembro y el estado general del paciente, hasta hacer necesario desde la amputación transmetartasiana hasta cualquier otra a un nivel superior.

Realizada la amputación, el muñón resultante pasa a ser el heredero del mismo déficit sensorial con similar problemática y por ello la adaptación de prótesis obliga a extremar las exigencias en cuanto a un ajuste y distribución de fuerzas en la cuenca, alineación, suspensión, educación del paciente y entrenamiento prostésico. Si a esto agregamos la deformidad frecuente en el otro pie y las alteraciones funcionales en manos, comprenderemos lo complejo del problema y porque, a diferencia de otros pacientes, el enfermo de lepra amputado requiere un prolongado período de trabajo.



Fig. 1: Ulcera plantar no controlada.

Los autores en esta exposición quieren enfatizar por último, el hecho de que no pretenden dar normas de trabajo en este campo y que comprenden que el abordaje y solución del problema del enfermo de lepra amputada ha de depender de los diferentes recursos disponibles en cada país.

Casuística

Para el presente trabajo los autores estudiaron 33 enfermos de lepra amputados cuyo análisis general aparece en los siguientes cuadros:

CUADRO I: CASOS AMPUTADOS Y SEXO

Sexo	Número
Masculino	26
Femenino	7

CUADRO II: CASOS AMPUTADOS: LATERALIDAD

Lateralidad	Número
Unilateral	25
Bilateral	8

CUADRO III: CASOS AMPUTADOS TIPO DE LEPRA

Tipo	Número
LL	14
LT	5
LI	10
LD	4

Cuadro IV:

Casos Amputados Según Tipo de Amputación y Utilización de Prótesis

Tipo de Amputación	Sin Prótesis	Con Prótesis	Total
Transmetatarsiana	6	—	6
Ricard	—	1	1
Syme	2	11	13
Por debajo rodilla	6	13	19
Por encima rodilla	2	—	2
Total:	16	25	41

CUADRO V:

Amputados Unilaterales

Trastorno Funcional en Otro Miembro	Sí	No
Pie	20	5
Manos	17	8

CUADRO VI:

Amputados Bilaterales

	Sí	No
Trastornos funcionales en manos	6	2

El Muñón y sus Problemas

Los problemas del muñón que encontramos en el enfermo de lepra tienen su origen común en el ataque específico a la piel y sus anexos y en la infección crónica que en los años previos se ha mantenido.

El ataque específico a la piel destruye su arquitectura normal, las glándulas sodoríparas y sebáceas, los folículos pilosos, y las finas terminaciones nerviosas responsable de la captación y transmisión de los impulsos sensoriales. Esto nos deja una piel más débil a la agresión de factores externos y desprovista del maravilloso sistema de alarma que representa la sensibilidad.

La infección crónica se constituye por otra parte en el aliado más importante en la desvitalización de los tejidos desde la profundidad a la superficie, y cuyas consecuencias encontramos en el muñón a menos que se hagan amputaciones a niveles excesivamente altos. De esta manera pueden permanecer focos fríos de infección en el hueso y lesiones vasculares, especialmente del sistema linfático.

Así nos explicamos en el post-operatorio inmediato la aparición de necrosis, tanto más frecuentes cuanto más baja es la amputación y la ocurrencia de fístulas e infecciones que podrán ocasionar dehis-

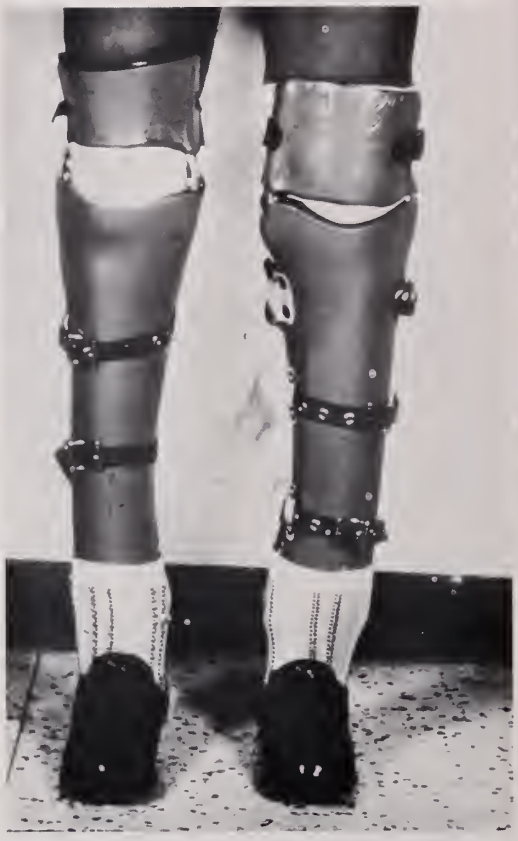


Fig. 2: Cuenca P. T. B. con puerta posterior, articulación de rodilla y manguito plástico al muslo (amputación de Syme bilateral).

cencia de la herida operatoria y retardarán la cicatrización. Igualmente la persistencia en algunos casos del edema post-operatorio del muñón puede explicarse en base a que no existe un libre drenaje debido a la esclerosis del sistema linfático, residual a linfangitis crónicas a repetición. Si recordamos además que estos muñones son insensibles al dolor, comprenderemos cómo estos pacientes fácilmente lo traumatizan y lo colocan en mala posición con todas sus consecuencias. El vendaje del muñón debe hacerse con cuidado para evitar complicacio-

nes que como necrosis circunscritas, pueden ocurrir por ser el paciente incapaz de alertar sobre un vendaje excesivamente apretado, como es incapaz también, por sus frecuentes lesiones en manos, de reajustarlo cuando se afloja haciendo así más difícil y prolongado el proceso de retracción del muñón. Estas consideraciones explican el porqué en estos pacientes el período preprostésico es más prolongado que en los amputados por otras causas.

En nuestros casos ha sido excepcional el desarrollo de neuromas y los pocos observados han sido en amputados por debajo de la rodilla. Así mismo la sensación fantasma ha sido rara y nunca hemos observado dolor fantasma, lo cual debe guardar relación con los trastornos neurológicos propios del enfermo de lepra.

Es así como llegamos a la etapa prostésica con un muñón que se caracteriza fundamentalmente por ser frágil, anestésico, atrófico y flojo.

Prótesis, Tipos y Modificaciones

En la elaboración de las prótesis se han utilizado los mismos materiales de uso común sin que tengamos preferencia por alguno en particular, y los tipos clásicos de prótesis se han modificado a fin de lograr una mejor distribución de presiones de acuerdo a los casos, y disminuir así las posibilidades de lesión a los tejidos blandos.

En las amputaciones transmetatarsianas nos hemos contentado en general con rellenar el calzado, colocar una almohadilla escafoidea y disminuir la altura del tacón a fin de distribuir más uniformemente las presiones en la planta y disminuir la descarga en la parte anterior del muñón.

En las amputaciones de Syme hemos utilizado principalmente los siguientes tipos y modificaciones:



Fig. 3: P. T. B. con ventana anterior y pie SACH en dorsiflexión (amputación Syme).

1. Cuenca cerrada sin áreas especiales de presión y suspensión P.T.B., utilizadas en casos que pueden tolerar descarga total al extremo del muñón y que exigen mejor condición estética.
2. Cuenca con puerta posterior, apoyo en el tendón rotuliano, pie SACH y articulación mediotarsiana, para obtener descarga parcial en el extremo del muñón suplementada por descarga en el tendón rotuliano y disminución de la presión en la parte anteroinferior del muñón durante la marcha.

3. Cuenca P.T.B. con ventana anterior y pie SACH en dorsiflexión. Se obtiene descarga parcial en el extremo del muñón y disminución de presión en la parte anteroinferior del muñón y en la cresta tibial.
4. Cuenca P.T.B. con puerta posterior, articulación en rodilla, manguito plástico al muslo y pie SACH. El manguito mantiene cierto grado de flexión en rodilla y disminuye la presión en la cresta tibial deforme. Hay descarga parcial en el extremo del muñón.

En las amputaciones por debajo de la rodilla, en su mayoría y salvo indicación en contrario, hemos preferido siempre las cuencas de contacto total para evitar los edemas distales y las rémoras circulatorias. Los principales tipos y modificaciones utilizadas han sido las siguientes:

1. P.T.B. con articulación de rodilla y corset al muslo, que permite disminuir la descarga a nivel del tendón rotiliano y los condilos tibiales.
2. P.T.B. clásica. Muy bien tolerada en casos con buenos muñones.
3. P.T.B. con cuenca deslizante y corset al muslo. Disminuye la descarga a nivel del tendón rotiliano y cóndilos tibiales, a la vez que elimina la fricción entre la piel y la cuenca propiamente dicha. Es una de las modificaciones más útiles en muñones anestésicos.
4. P.T.S. (prótesis tibial . supracondílea). Aún cuando no necesita suspensión, da mayor estabilidad a la rodilla, evita su hiperextensión, disminuye la acción de pistón y es más estética, no hemos obtenido todavía los resultados deseados.



Fig. 4: Areas de mortificación.

Problemas de Adaptación

Los problemas de adaptación son los que lógicamente se derivan de un muñón en las condiciones que ya hemos descrito. Su minimización depende así básicamente de una máxima exigencia en los aspectos quirúrgicos y prostésicos.

Como ya hemos señalado, el otro pie casi siempre presenta defecto funcional el cual debe haber sido resuelto previamente, máxime si consideramos que el mismo estará sometido a una sobrecarga. Asimismo las manos habitualmente exhiben defecto funcional que entorpece el entrenamiento pre-prostésico, y que es obligante conside-

rar cuidadosamente al hacer la prescripción.

Particular importancia reviste la educación del paciente que ha de iniciarse precozmente en lo relativo al cuidado del muñón, mantenimiento de la prótesis y su correcta colocación. La existencia de arrugas en las medias, cuerpos extraños en la cuenca, inadecuado ajuste al muñón, etc. deben ser detectados por el paciente mediante una conciente substitución de su sensibilidad perdida.

Poseyendo un muñón anestésico, el paciente no está en condiciones de señalar la sintomatología subjetiva indicadora de un inadecuado ajuste. Esto obliga a extremar la observación tanto por parte del equipo como por el paciente mismo y explica la frecuencia con que, a diferencia de otros amputados, la marcha es casi normal desde el primer momento. Esto, lejos de ser motivo de entusiasmo, debe ser tomado con cautela ya que es la mortificación de los tejidos en el muñón, un índice ya indeseable del correcto o incorrecto ajuste de la prótesis. Por ello se impone el revisar el muñón con muy cortos períodos de intervalo y aún así se producen lesiones en la piel cuya cicatrización hay que esperar antes de continuar el trabajo de adaptación, alargándose por lo tanto este período.

Las áreas de mortificación que sugieren modificar la distribución de presiones deben ser cuidadosamente analizadas, ya que fácilmente se reproduce el problema en otro sitio pudiendo hacer interminable el proceso de adaptación. A veces se justifica una alineación que no sigue los patrones establecidos pero que se traduce en una mayor protección del muñón.

Por último, aún cuando es un principio de trabajo que todos aceptamos, la adaptación de prótesis a un enfermo de lepra creemos requiere más que en cualquier otro caso, una estrecha cooperación y discusión conjunta de los problemas entre el médico, el técnico-prostésico y el terapista, y en fin de todo el equipo de rehabilitación.

Después de los expuesto y a pesar de las dificultades que implica la adaptación de prótesis al enfermo de lepra amputado, creemos haber obtenido algunos resultados prácticos en nuestra corta experiencia y esperamos que esta información pueda ser de utilidad a quienes tengan oportunidad de trabajar en este campo.

Conclusiones

La úlcera plantar es una expresión inespecífica de sufrimiento tisular traumático en un pie kinético con parálisis de musculatura intrínseca y trastornos de sensibilidad plantar.

Las amputacione del miembro inferior en el enfermo de lepra tiene su origen en el proceso destructivo por infección secundaria a partir de la úlcera plantar no controlada.

Con fines funcionales y de adaptación prostésica consideramos como tipos útiles de amputación las transmetatarsianas, la de Syne y las realizadas por debajo de la rodilla en el tercio superior de la pierna.

El post-operatorio inmediato puede complicarse debido a los residuos dejados por la infección crónica y el ataque específico a los nervios y estructural a los tejidos blandos.

El muñón resultante es el heredero directo del problema original y se caracteriza por ser en general frágil, anestésico, atrófico y flojo.

La prescripción de prótesis debe tomar en cuenta las alteraciones funcionales en manos, una amplia distribución de presiones y una máxima protección del muñón.

El déficit funcional del otro pie cuando existe, debe ser corregido previamente.

Es de máxima importancia una adecuada y precoz educación prostésica del paciente.

Aún cuando el período de adaptación de la prótesis es de por sí prolongado, se impone, para evitar retardos innecesarios, la revisión permanente del muñón a cortos intervalos.

Las modificaciones en la distribución de presiones deben ser cuidadosamente pesadas antes de ordenarlas, y la cautela debe ser el mejor consejero.

Es fundamental, para un buen resultado prostésico, la íntima compenetración del equipo humano de trabajo en el problema que se maneja.

Resumen

Los autores hacen una comunicación preliminar de su experiencia con el enfermo de lepra amputado exponiendo en líneas generales el proceso patológico que lleva a la amputación. Analizan una casuística de 33 casos amputados en los cuales se han adaptado 25 prótesis y exponen los problemas fundamentales que se presentan en los muñones. Informan igualmente sobre los tipos de prótesis y las modificaciones utilizadas para obtener el mejor resultado funcional en los casos trabajados, y analizan por último los principales problemas que se presentan en el proceso de adaptación de las prótesis.

ELECTROMYOGRAPHY FOR DETERMINING TRIGGER MUSCLES IN SPASTICITY

Alfred Ebel, M. D.

Spasticity in spinal cord transection may be defined as an indiscriminate and disorganized response of decentralized effector neurons to inordinate afferent impulses (1). It is not our purpose to discuss the pathophysiologic process of spasticity which, to a large extent, is still not fully understood. Although a number of hypotheses have been advanced the exact mechanism still defies clarification (2, 3). In this presentation we plan to discuss a relatively simple diagnostic method which will enable the clinician to select on a rational basis the muscle or muscle group which appears to be an incitor or trigger of the clinical manifestations which we call spasticity.

Spasticity of a mild degree may be of benefit to the patient since it tends to maintain the bulk of the muscles which are paralyzed. Such mild muscle contraction is, as a rule, not disturbing to the individual and will not result in deforming contractures of muscles and joints. Mild spasticity is readily accepted by the patients and requires no treatment; indeed, it has been suggested that such mild spasticity is metabolically useful (4), Spasticity becomes a major problem when it is of such severity that it interferes with the patients ability to function. Spasticity of this degree may interfere with the patient's nutrition, with rest and sleep, and may, through unequal muscle pull, produce severe deformities of joints and contractures of muscles. Severe spasticity is furthermore an obstacle to the rapid healing of decubitus ulcers and will negate any attempt at closure by plastic surgical means. If uncorrected, such severe degrees of spasticity may actually become a threat to the patient's life and at best will interfere with his potential for rehabilitation. It is imperative, therefore, that effective steps be taken to alleviate severe spasticity by whatever means possible. Drug therapy is as yet quite unsatisfactory. Although a number of therapeutic agents have been proposed, none of them have proved effective in adequately controlling spasticity. While some tranquilizing drugs may reduce spasticity, they are generally unsatisfactory because the dosage which may be required

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to produce the desired relief often result in marked drowsiness or even somnolence. Conservative measures such as stretching by means of physical therapy, or relaxation of muscles through hydrotherapy or by the use of local cold may be effective in mild spasticity but are of no permanent value in the severely spastic patient. There remains but one approach to the control of this major problem of the patient with spinal cord transection or disease, namely some surgical procedure designed to inhibit or abolish the excessive response of the involved muscle groups. The surgical techniques which may be employed are rhizotomy, conusectome, peripheral neurectomy, tenotomy and myotomy. More recently, the injection of absolute alcohol intrathecally has found favor in the control of spasticity in patients with complete motor and sensory lesions including loss of bowel, bladder and sex function. Where the lesion is incomplete, or where bladder or sex function is functionally useful, specific areas of spasticity have responded to intrathecal injection of dilute phenol (dissolved in glycerol) at the appropriate level by producing a selective anterior rhizotomy. All of the surgical procedures are useful in one type of problem or another; the selection of the method, however, depends upon a thorough evaluation of the degree and nature of the spasticity and the degree of preserved function so that the problem of correction may be approached rationally and without creating greater neurologic loss than is necessary.

Abramson and Hirschberg (5) demonstrated that denervation of a spastic muscle may have a more widespread effect in reducing spasticity than could be attributed to the effect of denervation of the individual muscle itself. They postulated that the decrease in overall spasticity was the result of abolition of sensory feed-back from the denervated muscle to the transected distal

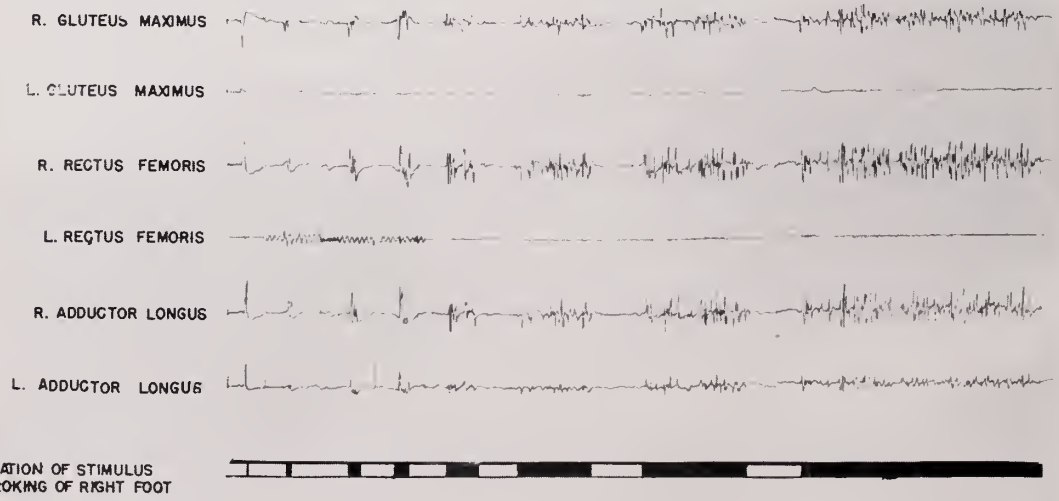


Fig. 1: (From Abramson and Hirshberg) Effect of left obturator nerve block in a case of spastic paraplegia. The spastic contraction of muscles on the left side of the body was greatly reduced.

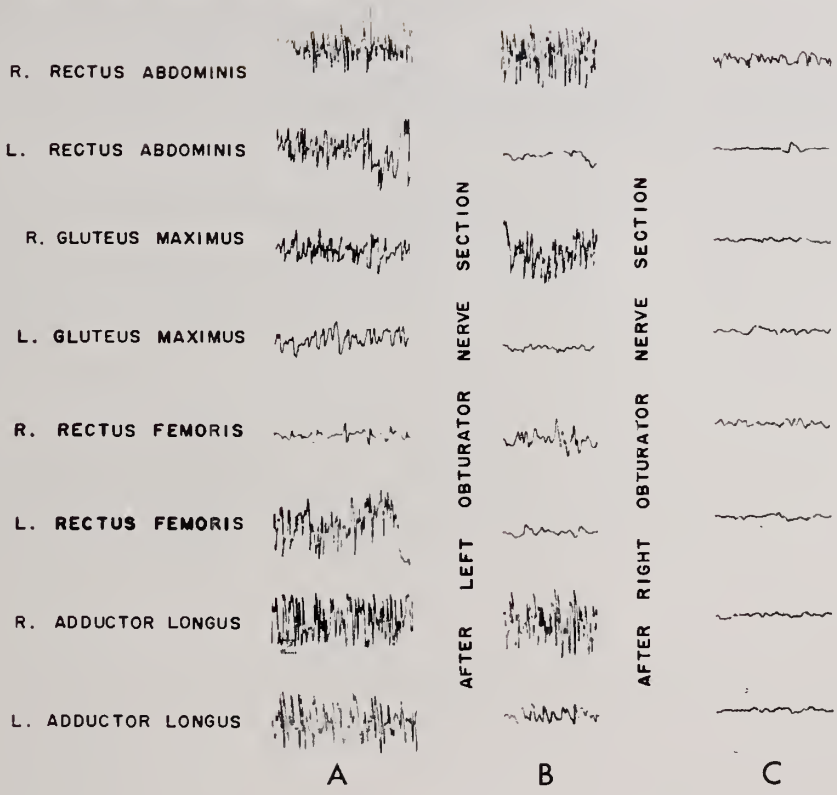


Fig. 2: (From Abramson and Hirschberg) Simultaneous electromyographic tracings taken from four muscles bilaterally in a case of high level cord lesion. A. Marked spastic contraction occurring in almost all muscles examined, in response to the stimulus of a deep breath. B. Spasticity greatly reduced on the left side in response to the same stimulus following left obturator nerve section. C. Spasticity greatly reduced on both sides in response to the same stimulus following bilateral obturator nerve section.

segment of the spinal cord. This decrease in afferent inflow was found to occur not only by paralyzing the offending muscle through peripheral neurectomy, but was also achieved when spastic muscles were rendered less spastic by tenotomy or myotomy, or where a muscle group became inactivated as a result of joint fixation through the formation of extra-osseous ossification. When such afferent inflow was diminished or abolished, overall spasticity became markedly reduced on the same side (Fig. 1). In patients with cervical lesions improvement was noted at quite a distance from the area where motor function had been interfered with. Thus they found that following ablation of both obturator nerves in a tetraplegic patient there was marked reduction of spasticity in the hands, abdomen, bladder and in the lower extremities (Fig. 2).

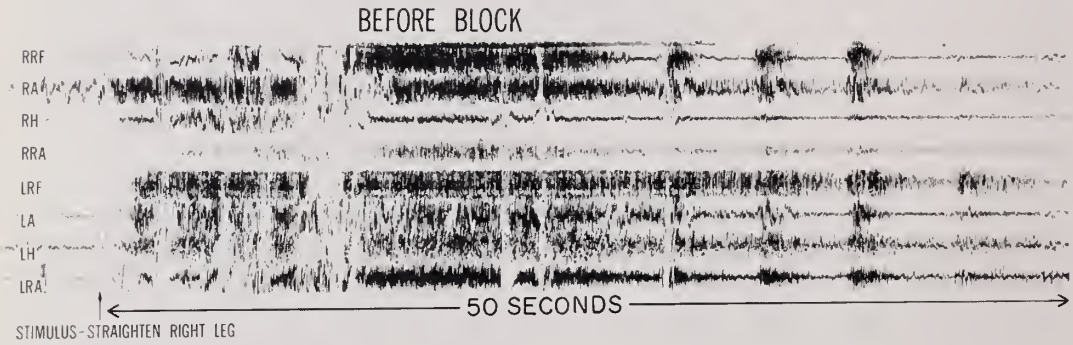


Fig. 3: Electromyographic tracing of four muscles bilaterally before block. Note prolonged spastic contraction of 50 seconds duration following stimulus of straig' tening right leg. Contraction most marked in right adductor and left rectus femoris muscles. RRF = Right Rectus Femoris; RA = Rigth Adductor; RH = Right Hamstring; RRA = Right Rectus Abdominis; LRF = Left Rectus Femoris; LA = Left Adductor; LH = Left Hamstring; LRA = Left Rectus Abdominis.

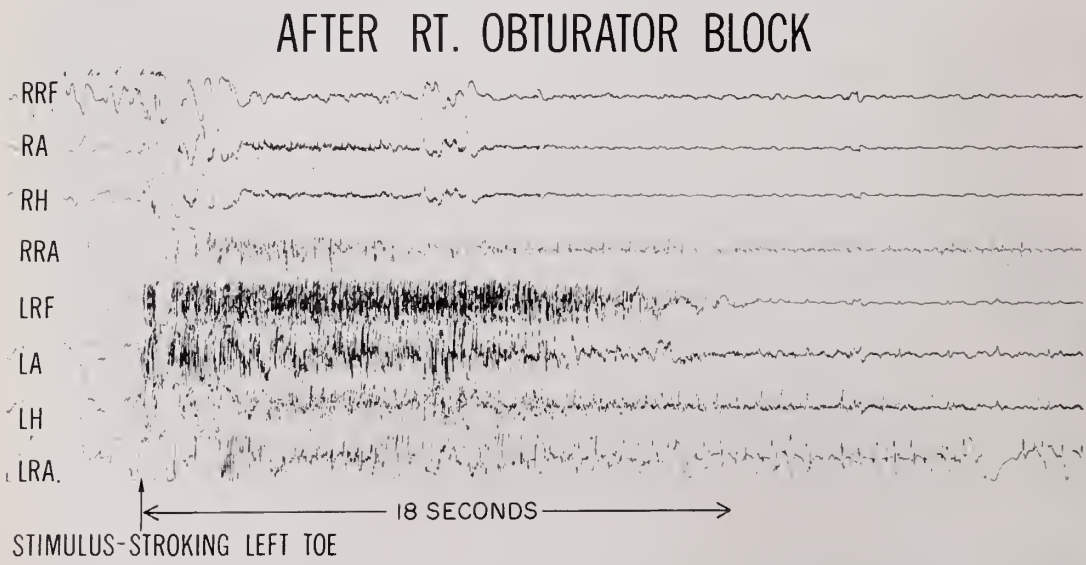


Fig. 4: Electromyographic tracings of same muscles as in Fig. 3, after right obturator nerve block. Note marked reduction of spasticity on left side, only 18 seconds in duration, and almost complete absence of spasticity on blocked side.

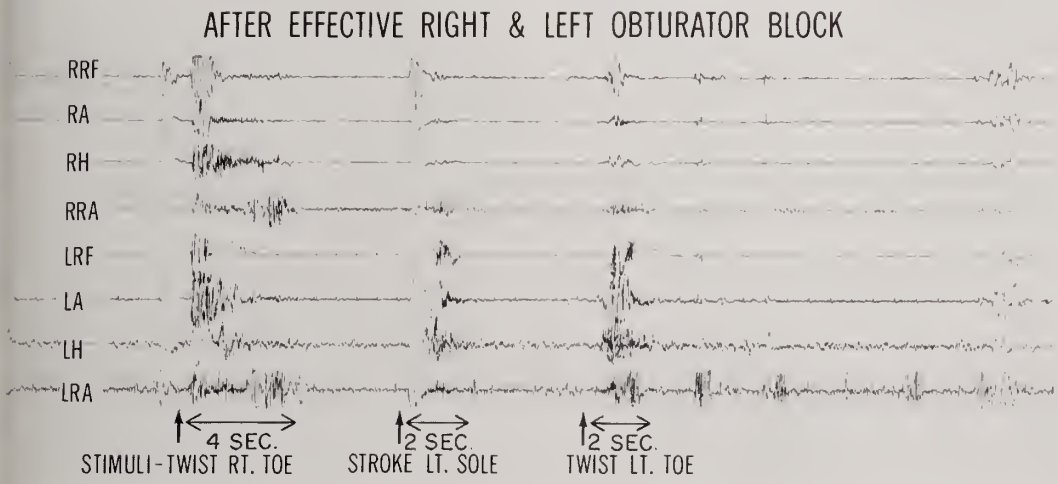


Fig. 5: Electromyographic tracings of same muscles as in Fig. 3, after right and left obturator nerve blocks. Note almost complete absence of spasticity following repeated sensory and proprioceptive stimulation. Duration of motor response 2-4 seconds.

From careful clinical observation of many patients with severe spasticity it has been noted that frequently one muscle group is the predominant trigger which sets off widespread spasticity. Since it is not always possible to determine by clinical examination alone the offending muscle group, we have utilized multi-channel electromyographic recording for the purpose of detecting the muscle showing the greatest amount of electrical activity and which, following denervation, myotomy or tenotomy might be expected to produce the greatest degree of clinical improvement in spasticity.

The technique is simple and the required equipment is available in almost every good hospital. Coaxial electromyograph needles are placed into selected muscles bilaterally. The number of muscles to be probed depends upon the equipment which is available. Since most hospitals have an eight channel electroencephalograph apparatus, four muscles can be examined bilaterally. With the newer machines providing sixteen channels, up to eight muscles may be tested bilaterally at one time. The selector switch on the electroencephalograph apparatus is placed on the EMG setting and electromyographic tracings are obtained with the patient completely at rest and the following simple stimuli such as stroking the foot, moving the great toe, stroking the skin of the abdomen or abducting the hip. The degree and duration of the spastic response is recorded on paper tape, usually at a paper speed of 15 mm/second and at calibration of 50 uv/5mm amplitude. The muscle with the greatest amount of electromyographic activity is then blocked by means of procaine nerve block. After an appropiate time interval to permit the anesthetic to become effective, the electromyographic examination is repeated, using the same stimuli. The contra-lateral muscle is

then similarly blocked and the electromyographic examination is again repeated, noting the response to the various stimuli and noting particularly the amplitude and the duration of the motor response in the various muscles to each stimulus. Observation of the electromyographic response following an effective nerve block will usually provide a rather reliable indication of what may be expected from a permanent denervation accomphished surgically (Fig. 3, Fig. 4, Fig. 5).

By utilizing this method the clinician and surgeon can identify more accurately the muscle which contributes most to the spastic state and can approach the task of surgical intervention with fairly definite assurance of the therapeutic response which may be anticipated. In spinal cord disease spasticity is usually present bilaterally. Since it has been shown that operation on one side will as a rule produce significant improvement on that side only, and since unilateral denervation may produce unequal muscle action with resultant deformity, these surgical procedures should always be carried out on both sides, although not necessarily at one sitting.

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PREVENTIVE ASPECTS IN REHABILITATION OF THE DIABETIC AMPUTEE

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Effective management of the diabetic amputee requires close collaboration between the physiatrist and his medical as well as paramedical colleagues. The need for multidisciplinary management has been demonstrated so effectively in rehabilitation of patients handicapped by neuromuscular and skeletal disorders that this approach now is established as essential.

Amputees now have available multidisciplinary clinics in which a physical therapist, occupational therapist, social worker, psychologist, vocational guidance counselor, prosthetist all work together under the guidance of the physiatrist. The special lifelong problems of the diabetic amputee, however, still do not often enough receive the required specialized attention. The life time medical needs imposed upon the amputee by the presence of diabetes make mandatory that close collaboration exists from the very onset between the physician who manages the rehabilitation process and the physician who is responsible for control of the metabolic disorder, maintenance of circulatory integrity of the remaining lower limb, and prevention of its loss through oversight or outright neglect. In addition, the diabetic who has lost one leg because of vascular pathology often also has other

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Increasing Magnitude of Problem

The number of diabetic amputees has increased. It is expected that this increase will accelerate. The discovery of insulin and advances in medical management have increased the life span of the diabetic and this increase has brought a number of problems. The expected longevity among adult diabetics prior to 1922 was said to be 2 years. At present, it is three-quarters of the expected life span of non-diabetics. Prior to 1922, diabetic coma was the chief cause of death. The diabetic now dies of late complications and not of his disease. With proper control, the diabetic can help prevent these complications.

The causes for death of diabetics have changed so remarkably that plans for management of the disease have been radically altered. Tuberculosis which undoubtedly was responsible for death of half the patients sixty years ago has now dropped to less than 0.2% Diabetic coma has fallen from

64% to 1%. Vascular disease of the heart, brain, and kidneys is now responsible for at least 75% of the deaths. Due to longer lives of diabetics, cancer has risen to 11.3%. associated disorders. He may have at the same time arteriosclerotic cardiac disease, renal disease, retinitis, and most likely impaired circulation of his remaining extremity. The collaborative medical management program of the diabetic amputee properly should begin before the surgeon amputates, continue through the post-operative preprosthetic period and on through prosthetic training into the long term follow up. Such a prolonged closely integrated program is necessary in management of the diabetic amputee.

Need for Patient Education

This increased longevity brings with it not only different causes of death, but an increase in the number of disabling complications that are incapacitating but not necessarily death producing. To prevent these complications, courses of instruction for the patient are necessary. Rehabilitation centers should have classes where a knowledge of diabetes and how to control it can be taught to the inpatients, their families, out-patients and those diabetics living in the vecinity of the hospital.

It is not enough for us to prescribe a prosthesis and train the patient in its use. We must make certain also that the patient knows how to prevent further complications leading to loss of the remaining limb.

The importance of this aspect of the problem is illustrated by a study (1) showing that 30% of a series of 294 diabetic amputees required amputation of the remaining leg within a period of three years. Fifty-one percent required the second amputation within five years.

lated to diabetes or simply due to intensification of ordinary arteriosclerosis. Goldenberg in 1958 described peripheral vascular lesions similar to those found in diabetic glomerular renal lesions and vascular lesions of eyes from diabetics (3). Sipersteen et al in 1966 demonstrated increased width of muscle capillary basement membrane in diabetic and prediabetic patients (4).

In Goldenberg's cases, it was interesting to note that in 1/3 of their diabetic cases with gangrene, palpable pulses at 11 common points of palpation had been reported clinically. In 10% of such cases, pulses were as strong as on the unaffected side. The nondiabetics gangrenous specimens rarely had a history of having had patent pulses. Goldenberg reported also that the gangrene found in the diabetics more commonly had a patchy distribution. This together with the patent pulses appeared to indicate that in diabetics, gangrene may occur without occlusion of one of the main arterial trunks.

Most observers report that the great majority of diabetic patients with peripheral occlusive arterial disease display a so-called mild form of diabetes, as defined by minimal insulin requirements. Nonetheless, gangrene of the lower extremities is much more common in the diabetic than the nondiabetic. Since the lower extremities are the weight bearing, load carrying, work horses of the body, disease here necessitates bed or chair confinement.

As Warren and Le Compte have pointed out (5) when there is progressive narrowing of the lumen of an artery, there is time for collateral circulation to develop. While there may be pain and disability

during the process of readjustment, eventually a delicate point of equilibrium is

Pathology

These figures are not surprising when one considers the pathologic findings. Bell in 1950 analyzed the post-mortem records of 28,240 males and 15,119 females more than 10 years of age (2). He demonstrated the remarkable effect of diabetes in intensifying and accelerating gangrene. He concluded that if only gangrene due to arteriosclerosis is considered, gangrene develops nearly 40 times as frequently in diabetics as in nondiabetics.

There is controversy as to whether the vascular complications are due to a specific disseminated vascular disease directly reached. Here, the combined blood supply from both cognate system vessels and collaterals is just sufficient for the ordinary needs of the limb. Any unusual stress may tip the balance. In the final analysis then, the state of the smaller arteries, upon which the establishment of a collateral supply is dependent, is the principle determining factor.

The unsettled status of the problem of the specificity of diabetic vascular disease is illustrated by the report of Strandness (6). He and his colleagues failed to find any consistent or significant differences in severity of diabetic or nondiabetic arterial disease, and were not able to substantiate the specific lesions of the small arteries or arterioles reported by Goldenberg. The major difference found by Strandness was the presence of a peripheral neuropathy in 27% of diabetics and none in nondiabetics. Also the pattern of occlusive involvement of major arteries is distinctly different in the amputated extremities of the diabetic and nondiabetic. The diabetics had a higher incidence of involvement below the knee in the anterior tibial, posterior tibial and peroneal arteries. Thus, the diabetics had quantitatively more extensive major artery obliterative disease below the knee than the non diabetic. The diabetic then, if this is true, has a greater reduction of peripheral blood flow and more ischemia below the knee than does the nondiabetic.

The diabetic limb is subject to double jeopardy since it has the same incidence of involvement of the femoral-popliteal arteries as the nondiabetic but more extensive vascular involvement below the knee. The extensive involvement below the knee forces blood through smaller vessels with higher resistance pathways which are much less effective than the geniculate vessels about the knee or profunda femoris in the groin.

Diabetic Peripheral Neuropathy

Of great importance found by all workers is the peripheral neuropathy in diabetic amputated extremities. Sensory modalities are more more frequently affeted in the diabetic and give rise to unrecognized indolent ulcers that often lead to gangrene and amputation. The impaired sensation often present as result of the peripheral neuropathy accompanying diabetic peripherial vascular disease poses a special problem. The diabetic develops small breaks in the skin that would be noted by others, but is unnoticed by the diabetic patient. The diabetic must be instructed to search for skin abrasions and give them proper attention. Such skin breaks become infected if not carefully cleaned and covered with sterile gauze. Such unnoted small skin breaks can be the forerunner of an amputa-

tion. The diabetic must be instructed to examine his remaining foot and leg in a bright light. He must be taught how to carefully examine it daily. If impaired vision also is present, he should have someone knowledgeable with good vision inspect and help him keep his foot from becoming the site of a skin break or infection.

Long Term Management

Sufficient attention and emphasis have not been placed upon a preventive program essential for the continued vitality of the remaining lower limb of the diabetic amputee. The diabetic amputee remains a diabetic. His metabolic problems, his obesity, arteriosclerosis and neuropathy, the threat of painless infection and gangrene that led to loss of the first limb remain as threats to the second limb throughout the patient's existence. The diabetic amputee who has lost one lower extremity requires the most intensive type of a preventive management program to avoid loss of his remaining limb.

The management of the diabetic amputee might be divided into:

1. The general management of the arteriosclerotic diabetic
2. Education of the diabetic patient
3. Prophylaxis against gangrene

The general management should pay particular attention to careful lifetime control of the metabolic problem with diet and, if necessary, insulin or oral agents. The diet should contain at least 1 gram or protein per kilogram of body weight and if possible 10-20% more, especially in the geriatric patient. The usually associated obesity should be managed. If neuropathy is present, vitamins, especially B-1 and B-12, may be needed. The details of this program require that the patient have a physician who will medically be his mentor and give him the personal attention and support essential for a custom-tailored lifetime diabetes control program.

The patient's full intelligent cooperation is essential. The patient and members of his family should be taught how to manage the diet, insulin, oral hypoglycemic agents, urine examinations, and care of the remaining lower extremity.

This brings us to the second important phase of management—education of the diabetic patient. Rehabilitation is essentially a learning process in which the physician and his colleagues teach the patient how to more effectively adapt to life in modern society despite some physical and physiological impairments. Diabetes is a lifelong disorder for which the patient makes many decisions regarding food, activity, insulin, based on knowledge of the disease and its treatment. When he has suffered the loss of a limb, he must add to this fund of knowledge considerable information concerning what to do and what not to do about his remaining leg.

To manage this problem we have found, as Joslin had recommended, that a formal series for group instruction to diabetic amputees and their families was most helpful. To this group we have invited other diabetics in the hospital, diabetic outpatients, and diabetics in the neighborhood. Their families are also invited. They receive instructions as a group at regular intervals. The subject matter follows a checklist prepared by the American Diabetes Association. The material covered includes diet, urine testing, action of insulin and other hypoglycemic agents, technique of in-

sulin injection and sites used, care of syringe and of insulin, symptoms of hypoglycemia, symptoms of uncontrolled diabetes, care of the feet and what to do in case of acute complications. As a result of knowing these basic facts, the diabetic is betters controlled, more cooperative, can avoid complications and hospitalizations, and may live longer.

Involved are four instructors—physician, nurse, dietician, and podiatrist. This group covers the curriculum as recommended by the American Diabetic Association and expounds in detail on each.

The third aspect of the preventive program was touched upon in the educational program—prophylaxis against gangrene. Gangrene typically occurs in the elderly with mild diabetes of long duration and inadequate diabetic treatment. To preserve the remaining leg, it is essential that the patient give strict attention to his feet.

This foot program is designed to maintain foot hygiene, prevent abrasions and infections of the skin, manage corns, and callouses properly, and treat the imperfect circulation.

The balance that nature has achieved with collateral circulation to meet the vital need of the tissues of the remaining foot and lower extremity is a delicate one and can easily be tipped. Associated with this is the presence of peripheral neuropathy in about 1/3 of these patients so that injuries or abrasions which might predispose to infections are not suspected by the patient.

Thus the physician and his patient must be continously aware of a whole list of dangers: heating pads and hot water bottles; strong linaments; new shoes; careless trimming of corns and toenails; epidermophytosis; sitting with knees crossed or wearing circular garters.

The following are helpful for insufficient circulation with cold feet:

1. Exercises—such as foot bending on a regular schedule
2. If there has been an amputation, keep off the feet 15-20 minutes each hour.
3. Massage with lanolin or cocoa butter
4. Wear long white woolen socks at night and use soft white woolen socks in cool and cold weather

The well known rules of hygiene for the feet must be followed. The feet should be washed daily with soap and lukewarm water, then dried thoroughly but gently. When dry, apply lanolin to keep skin soft. Toe nails are cut only after bathing when they are soft and only straight across and only in a good light. Overlapping toes should be separated with lambs wool. Pointed, poorly fitted shoes are to be avoided. All patients over sixty years of age should have daily rest periods with the shoes removed. Feet should be carefully examined each Sunday morning. Bedroom slippers should not be worn in place of shoes. patients should avoid stepping on floor with bare feet.

Callouses and corns are common and frequently are the site of an infection which can lead to osteomyelitis. These lesions come from pressure from excessive body weight, from badly fitting shoes or a combination of both. A neuropathy will prevent awareness of pain when the callouses and corns become infected.

Patients should be warned against cutting such lesions with a sharp instrument. Strict cleanliness, relief from pressure, drying of the skin, and periodic supervision by a trained chiropodist are important.

In regard to treatment of skin abra-

sions first aid treatment is of utmost importance even in apparently minor injuries. A physician should be consulted at once. Iodine and strong antiseptics should be avoided. Use of the abraded foot should be limited as much as possible. It should be kept slightly elevated.

Any discussion of treatment of peripheral circulatory insufficiency would be incomplete without mention of Buerger's Exercises which are very useful and often overlooked. Buerger's Exercises should be utilized as a daily routine.

Conclusions

Efforts at long time close management to protect the remaining limb of the diabetic amputee are necessary. These efforts must be custom tailored to meet the individual needs of each patient. The physiatrist has an important role in long time follow up, but must collaborate in this effort with the diabetic's personal physician, the podiatrist, and when necessary, with the surgeon. The diabetes must be controlled; the obesity must be overcome; the vascular reserves of the remaining limb must be maintained and, if possible, improved. Repeated examinations to watch for the threats enherent in abrasions, infections, injuries, as well as the dangers from lack of sensory protection because of diabetic neuropathy must be kept in mind. The patient must be educated and supported in this effort if the remaining extremity is to avoid meeting the same fate than befell his first lower extremity victim of diabetic gangrene and amputation.

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FUNDAMENTALS OF THE PHYSIOLOGY OF THE GAMMA MOTOR SYSTEM

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It has been known for a long time that the striated muscle in animals and man contains not only the regular muscle fibers but also special fibers which, while contractile, do not contribute to the visual contraction of the entire muscle. Onanoff in 1890 (1) showed the first evidence that this special organ called the muscle spindle basically functions as a sense organ rather than as a producer of motor activity. This was confirmed in 1894 by Sherrington (2). Understanding of the function of the muscle spindle did not develop much until the work of Granit and his co-workers (3). They showed that the muscle spindle together with the tendon organ is a major sense organ of propriocepsis.

Reflexes from the muscle and other peripheral receptors have long been divided into two major categories — the monosynaptic reflex and the multisynaptic reflex. Monosynaptic impulses through the spinal cord show delay above the normal conduction velocity of one-half millisecond. This delay is well known as the synaptic delay. The interesting point therefore is not that the impulse undergoes a delay in the spinal cord but that the delay is no longer than one synaptic delay. Therefore the conclusion is drawn that these impulses pass through the spinal cord through only one synapse which therefore logically must be located at the anterior horn cell (4, 5). Reflexes of this type find their origin in impulses coming from the muscle and tendon organs.

In contrast to this, multisynaptic reflexes come not only from sense organs in the muscle but also from skin receptors (5). They pass through the spinal cord with several synaptic delays. The action current in the anterior root is much more drawn out and contains several spikes in contrast to the single spike of the monosynaptic reflex.

The structure of the muscle spindle consists essentially of two contractile elements between which is located a sensory organ, the so-called nuclear bag from which a sensory fiber originates, variously called the nuclear bag fiber, or the annulo-spiral fiber or the type I fiber (6). This is a large

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and fast conducting fiber. A second sensory fiber is found originating from sensory endings in the muscular area and is labeled as a number II fiber. The endings are the flower-spray endings (7). This is a much thinner and slower conducting fiber. Previous controversy as to whether the flower-spray endings could be motor rather than sensory (8) has been settled by evidence showing that the flower-spray endings while occurring in the same area as the motor endings to the spindle fibers can be definitely separated from the motor innervation and are undoubtedly sensory. The motor innervation of the spindles occurs through small fibers, the so-called gamma fibers, which have their own gama motor neurons in the spinal cord.

The major difference in physiological function between the tendon organ (Golgi organ) and the spindles is in their behavior and different response to stretch and contraction (9). When a muscle is stretched, both the tendon organ and the spindle organ are stretched and therefore send up impulses to the spinal cord. When the muscle contracts, the Golgi organ (being in series with the contractile elements of the muscle) is again stretched. In contrast to this, the muscle spindles which are parallel to the contractile element of the muscle will relax and any spontaneous activity in the muscle spindles will decrease. This can be used to differentiate between the sensory output of the Golgi organ and the muscle spindles. During stretch both the Golgi organ and spindle organ fire. During contraction the Golgi organ fires and the output of the spindle organ is reduced to a very low value or to zero.

Very important is the fact that by contraction of the spindle fibers the reaction of the spindle organs can be altered. During contraction of the muscle the slack of the spindle can for instance be taken up (10). The output of the spindle organ becomes the algebraic sum of the contraction of the normal motor fibers (extrafusal fibers) and the spindle fibers. In this way the central nervous system can also adjust the sensitivity of the sense organs to contraction and stretch by inducing contraction into the spindle fibers. This very important phenomenon is called spindle bias (11). Experimental evidence for a spindle bias can be shown as follows: When the increase in spindle output is plotted as a function of length, de-efferentation makes very little difference in the output. However when the muscle is deafferented, a considerable decrease in output occurs. The spindle function then appears to be dependent on motor outflow to the spindles and not on sensory inflow into the spinal cord.

It has been shown that multiple connections exist between the motor neurons of the extrafusal fibers and those of the spindles and the sensory input from the Golgi organs and the muscle spindle sensory organs. Monosynaptic testing techniques using the principle of the subliminal fringe have been used to test the effect of the muscle sense organs on the excitability of the motor neurons (5). If a muscle is made to contract, resulting in activity of the Golgi organ and relaxation of the spindle organ, it is found that the motor neurons of the muscle and its synergists are inhibited (12). Similarly it could be shown by Granit that activity of the Golgi organ facilitates the motor neurons of the antagonists (13).

Stimulation of the muscle spindle organ (by stimulation of a few gamma motor fibers gives a different result (14). During

stimulation of the spindle organ without muscle contraction the sensory influx from the spindles facilitates the motor neurons of the muscle and its synergists and inhibits the motor neurons of the antagonists. Between the Golgi organ and the spindle organ there is therefore a double reciprocal innervation which shows a fairly high degree of symmetry.

However, simultaneously with the monosynaptic reflexes from the spindle organ it can be shown that multisynaptic reflexes occur which are inhibitory to the synergists (13). These reflexes however are not symmetrical like the monosynaptic reflexes. They seem to show a preference for flexion. They have a general facilitatory effect on the flexors and an inhibitory effect on the extensors. Obviously this has considerable importance in posture and locomotion (15).

It has been shown that during the initiation of spasticity, spindle activity precedes the activity of the muscle fibers. Again when spasticity is suddenly interrupted, the spindle fibers become highly active. The relaxation of the muscle tends to decrease activity in the spindle fibers and a simultaneous activity of the spindle fibers themselves tend to increase it. As a result of these two opposing influences an oscillatory phenomenon can occur in the spindle at the time of relaxation (3, p.243). The clinical significance of this phenomenon is at the present only very poorly understood.

In several phenomena it has been shown that the activity previously known as motor function is preceeded by activity of the spindle system. An example of this is Sherrington's lengthening reaction. When in a decerebrate animal a muscle is slowly stretched, activity occurs first in the spindles which is then followed by activity in the muscle fibers themselves. When during the intense stretch the breakdown of tension occurs, spindle activity disappears first followed by the disappearance of the activity of the muscle fibers themselves (10). Hagbarth (16) has shown that stimulation of the skin over a muscle facilitates spindle activity and motor activity while stimulation of another area of the skin can produce inhibition. Records of this experiment show that facilitation occurs first in the spindle system preceeding the activity of the alpha motor system (17).

A very interesting insight into the physiology of the tonic neck reflexes can be obtained from the experiments of Eldred, Granit and Merton (10). These authors showed that if spindle activity is recorded simultaneously with motor response of the normal tonic neck reflex, spindle activity preceeds motor activity. It has been well known for a long time that tonic neck reflexes disappear after cutting of the dorsal roots. However under these circumstances, spindle activity continues while motor activity disappears. This finding allows several conclusions which can be of major importance for our clinical understanding of movement and therapeutic exercise. First, they show that something can occur in the muscle without visible contractile activity. This could be of considerable importance in explaining muscle re-education and the effect of muscle re-education on the zero muscle and of several other phenomena in therapeutic excercise. Secondly, they show that it is at least possible that spindle activity initiates motor function. Possibly it could be suggested that in an initiation of movement spindle activity occurs first through the gamma motor system. Following this, impulses from

the spindles reach the spinal cord and there combine with other impulses from the cortex to the alpha neurons to produce visible movement.

It is becoming increasingly clear that for the development of normal movement good coordination and correlation between the alpha and gamma motor systems are essential. It is possible in animal experiments to decouple the alpha and gamma motor systems. One of the major consequences of this uncoupling is a very severe degree of incoordination. It has been suggested that much of the coupling between the two systems occurs in the reticular substance. As is well known the reticular substance is an area where sensory impulses from many sense organs come together (18) to provide impulses for the cerebral cortex which has a great deal to do with keeping the subject awake (Magoun's Awakening Reaction). This was first demonstrated by the famous experiment of Strümpell (19) who showed in a patient who had only a few sense organs left that covering of these sense organs immediately put the patient to sleep and removal of the cover immediately awoke the patient.

To validate the concept that movement may be initiated by spindle activity several additional data are necessary. The first question that should be answered is whether cortical innervation of the spindle system can be shown. Mortimer and Akert (20) have shown that cortical innervation of the spindle system indeed exists. During their experiments cortical activation of the spindle always preceeded motor function. They could also show that localization of the gamma motor system in the cortex exists as it does for the alpha motors system. Of equal importance is the work of Partridge (21) who shows that in simple movements, timing relations can be explained best on the basis of the setting of spindle bias with a myotatic reflex superimposed upon it.

If it were correct to assume that the spindle system initiates voluntary movement, studies of the function of the spindle system in learning would be of considerable importance. Buchwald and co-workers have shown that conditioning in the spindle system can occur much more readily than in the motor system (22). In a naive cat with tones as conditioning stimulus and a pain stimulus as the unconditioned stimulus, gamma motor neurons begin to respond to the conditioned reflex in 10 – 20 trials, while the alpha system required a 100 – 200 trials. The latency in the gamma motor system is considerably shorter than in the alpha system (23). Most important, the authors found that when they blocked the gamma loop (by Flaxedil) no motor conditioning was obtained. However, if after enough stimuli to condition the spindle system the block was removed, conditioning of the alpha system proved to be much easier than in a naive animal (24). Therefore, conditioning of the gamma motor system is possible without functioning of the alpha motor systems. It is obvious that these experiments are of considerable importance to the realization of the value of the gamma motor system.

It has been shown that the gamma motor innervation varies a great deal from muscle to muscle. The tonic muscles are more heavily endowed with muscle spindles than the phasic muscles and the spindle system seems to have more importance for the tonic muscles (25). Evidently, these differences are not limited to properties of the peripheral muscles (26). The well

known experiments of Buller and Eccles (27, 28) in which they performed cross-union in a kitten between the nerves of a tonic and a phasic muscle showed that when the kitten became a cat the muscle which should have developed as a tonic muscle now had become phasic and the muscle which should have developed as a phasic muscle now had become tonic. Obviously, central nervous system patterns are an important part of this development together with the development of the peripheral sensory system (29).

It has been common, particularly among clinicians, to consider the muscle system primarily as a motor system. It is becoming increasingly obvious that the muscle system is also a very complicated sensory system which shows all the fundamental sense organ properties of other sense organs. Some of the properties that are prominent in the proprioceptive system, such as the centrifugal innervation of the muscle spindles, have been recognized in other sense organs such as the retina and the organ of hearing. Other well known phenomena of sense organ physiology such as the on and off effect of the retina have also been found in the sense organs of the muscle.

It appears that evidence is accumulating to show that the spindle system plays an important role in the initiation of voluntary movement. There are several points that need clarification and which tend to complicate the simple picture outlined here. Kuypers has shown that direct contact does occur between cells in the cortex and the anterior horn cells. These could not be found in the cat; they were much more common in the monkey and were very frequently found in the chimpanzee. The have also been recorded in man (30). These findings bring into focus the fact that many of the experiments done on lower animals cannot automatically be applied to our understanding of movement in man.

It is not yet clearly understood what the total muscle sense organ is. Certainly evidence has been presented that the joint receptors are a major part of the motor sense organ. How important this function is in man and what its clinical value is hardly understood at the present time. When extensive destruction of a joint and joint capsule occurs in disease there is some evidence of incoordination but not the amount of incoordination that one would expect on the basis of physiological experiments in lower animals. The concept of the total muscular system as a complicated sense organ is however an important one. The study of the function of the relation between this sense organ and the motor function together with the development of perceptual motor tests in humans is therefore an important field for clinical study.

In recent years it is becoming clear that the innervation of the spindle is a double system (31). There is a difference between the annulo-spiral endings and the flower-spray endings. Some of the difference may be mentioned here. The annulo-spiral fibers (I) are found in every spindle and only one to a spindle. The flower-spray endings (II) may be absent in the smaller spindles. The axons of the I endings are larger than of the II endings. The annulo-spiral endings are more sensitive than the Flower-Spray endings. However, above threshhold, the flower-spray endings produce more sensory output than the annulo-spiral endings. In the I fibers the discharge

rises rapidly and then falls to a tonic level. In the II fibers there is no overshoot. The I fibers show a sudden burst of activity during relaxation, the II fibers do not. Also there is more irregularity in the response of the I fibers than in the II fibers. There is a difference in adaptation rate between the two. It seems that I fibers are most responsible for facilitation of synergistic motor neurons and inhibition of antagonistic neurons while the II fibers seem to be more responsible for the asymmetry with pre-emphasis of the flexor motor neurons. There is some question whether there are on the motor side also two types of spindles — the nuclear bag fiber and the nuclear chain fibers. While this separation is not as clear as on the sensory side recent research tends to show evidence of these two types. Certainly the dual motor and dual sensory function of the muscle spindles needs elaboration and again the clinical significance of these findings at this time is hardly understood at all.

Summary

The muscular system has not only a motor function but is an important and complicated sense organ. The major sense organs are the Golgi organs and the muscle spindles while receptors in the skin and the joints contribute to the overall sensory function. An important property of the spindle sense organs is that the central nervous system can adjust the sensitivity of these organs through the establishment of spindle bias. The spindle system and the Golgi system appear to provide a double reciprocal system operating monosynaptic reflexes. Multisynaptic reflexes are possibly largely initiated by the flower-spray endings and provide asymmetry with preference towards the flexors. Evidence is accumulating that spindle activity may precede alpha motor neuron activity. Experiments on the tonic neck reflexes and on the conditioning of the spindle system and the evidence that the spindles have a direct cortical innervation seem to indicate the possibility that movement may be initiated by activity in the spindles, which would be followed by sensory outflow from the spindles into the spinal cord, which again would integrate with direct impulses to the alpha motor neurons to produce actual voluntary movement. The coordination between the alpha and gamma motor systems is extremely important. In animal experiments incoordination is the major result of the disturbance of this correlation. Several experiments on the spindle systems have shown that function can occur in muscle without visible contraction. The clinical significance of many of the physiological findings of recent years is only just beginning to become apparent. The difficulty of the evaluation of these physiological findings in terms of the clinical data is made more difficult by the problems of transfer of data obtained in animals to man.

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HEMIPLEGIA IN THE VETERANS ADMINISTRATION

Frank J. Schaffer, M. D.

It is a fairly well known fact that the vast majority of Americans who are hemiplegic have fallen heir to this most crippling disability via a cerebral vascular accident - or stroke. In the short time allotted me, my comments will therefore be focused on the latter entity, keeping in mind that stroke is the prime cause of hemiplegia and ranks only behind heart disease and cancer, statistically, as the cause of death in the U. S. A.

There are no reliable data on how many Americans have a stroke in a given year because unlike tuberculosis, for instance, health laws do not require physicians to report each case. There are no accurate figures concerning even those who have had strokes severe enough to leave them permanently paralyzed. The last available estimate indicates that there are about two million people in this country who have had one or more strokes of varying severity and that some three quarters of a million victims, chiefly in the 65 - 74 year old age group, are now added each year. As medical advances are made to extend the lives of our population we can therefore expect stroke figures to become larger. In the United States there are now approximately seventeen million people 65 years of age or older. It is estimated that five years from now - there will be 20 million in this age bracket.

Although this crippling and killing disease is slowly claiming increasing numbers of our citizen we are now becoming increasingly successful in delaying its dread touch until a later age than heretofore. Since 1950 the death rate of stroke victims in the 45 to 64 age group has dropped 22%. Such success stems from the continuing dramatic developments in the various disciplines of medicine. This in turn has wet our appetite for further investigation into this medical catastrophe and has promoted the whole hearted support of the Federal Government.

A good deal of our effort is now directed at stroke prevention. In this regard we deal, as early as possible, with predisposition to atherosclerosis, via weight control - low cholesterol diet, increase of physical activity; limiting use of tobacco and treatment, if present, of hypertension, diabetes, hormone disturbance and gout. A better understanding of hypertension, coupled

From the Physical Medicine and Rehabilitation Service, Department of Medicine and Surgery, Veterans Administration Central Office, Washington, D. C.

with today's medical and surgical treatment methods constitute a giant step forward in stroke prevention. Finally, the prevention or early and vigorous treatment of disease predisposing to embolism add to the control of precipitating causes of stroke.

In the matter of recovery from stroke - patients with "transient ischemic attacks", which group constitutes 25 to 35% of the total number of stroke victims, recover all function spontaneously in a matter of days or weeks. Furthermore, we have learned that anticoagulants are of value in stopping the advancement of "transient ischemia" to "progressing" and "completed strokes". On the plus side also is the knowledge that 25% of all strokes are due to occlusion of neck vessels and amenable to surgical intervention. Results of surgery in this group are classified as "good" in 75% of the cases.

Following are pertinent statistics from the U. S. Veterans Administration:

As of June 30, 1965, there were 21,673,000 living veterans of all wars and 161,000 peace time veterans. The average age of the 5,718,000 veterans that took part in the Korean Conflict was 35.9 years. Of the 14,969,000 WW II veterans it was 45.9 years. Of the 2,121,000 WW I veterans it was 70.9 years and of the 15,000 surviving Spanish American War veterans it was 87.1 years.

These figures concerning age of our war veterans take on special relevance when viewed in relation to the following statistics concerning cerebral vascular accident patients discharged from all VA hospitals during 1957, 1960 and 1964. The total number of patients discharged during these years were 477,095 in 1957, 511,930 in 1960 and 629,345 in 1964.

Case fatality rate in VA experience in 1957 for all patients with a *primary diagnosis* of cerebro-vascular accident (including para and quadriplegia) was 2230 out of a total of 7,560 patients, or 29.5% (Table I).

TABLE I: PATIENTS WITH C. V. A. DISCHARGED FROM VA HOSPITALS IN 1957

		Age Distribuition		
	Total	Under 55	55-64	65 & Over
Subarachnoid hemorrhage	355	240	80	35
Cerebral hemorrhage	1,230	235	500	495
Cerebral embolism and thrombosis	4,060	595	1,680	1,785
Stroke (not otherwise classified)	125	40	50	35
Cerebrovascular insufficiency	985	40	420	525
Hemiplegia, hemiparesis	55	40	10	5
Subtotal:	6,810	1,190	2,740	2,880
Chronic brain syndrome associated with arteriosclerosis	635	5	195	435
Total Classifiable as "Stroke":	7,445	1,195	2,935	3,315

TABLE II: PATIENTS WITH C. V. A. DISCHARGED FROM VA HOSPITALS IN 1960

	Total	Age Distribution Under 55	55-64	65 & Over
Subarachnoid hemorrhage	379	268	46	65
Cerebral hemorrhage	1,333	327	286	720
Cerebral embolism and thrombosis	5,086	923	1,128	3,035
Stroke (not otherwise classified)	19	2	2	15
Cerebrovascular insufficiency	1,447	111	305	1,031
Hemiplegia, hemiparesis	682	251	122	309
Subtotal:	8,946	1,882	1,889	5,175
Chronic brain syndrome associated with arteriosclerosis	2,552	60	499	1,993
Total Classifiable as "Stroke":	11,498	1,942	2,388	7,168

Case fatality rate in 1960 of 11,134 patients with a primary diagnosis of cerebrovascular accident was 2,672 or 24% (Table II), above.

Case fatality rate in 1964 of 14,643 patients with a primary diagnosis of cerebrovascular accident was 3,404, or 23.2% (Table III), below.

TABLE III: PATIENTS WITH C. V. A. DISCHARGED FROM VA HOSPITALS IN 1964

	Total	Age Distribuition Under 55	55-64	65 & Over
Subarachnoid hemorrhage	507	338	33	116
Cerebral hemorrhage	1,939	517	237	1,185
Cerebral embolism and thrombosis	6,914	1,379	987	4,548
Stroke (not otherwise classified)	24	4	3	17
Cerebrovascular insufficiency	2,545	343	353	1,849
Hemiplegia, hemiparesis	852	319	135	398
Subtotal:	12,781	2,900	1,768	8,113
Chronic brain syndrome associated with arteriosclerosis	4,331	138	361	3,832
Total Classifiable as "Stroke":	17,112	3,038	2,129	11,945

In comparing the figures of the totals classified as stroke in the above tables we note a progressive shift of morbidity to the group 65 and older. Specifically, the mor- 40% in 1957; 58% in 1960 and 63% in bidity rates for this older age group were: 1964. Fortunately, the mortality rate during these years showed a consistent downward trend. American medicine can take justifiable pride in statistics such as these, but by the same token we must prepare ourselves for the care and treatment of increasing number of geriatric long term chronic patients.

Research

The area of cerebral vascular disease research has been identified as an unique national need since present therapies still leave much to be desired, and basic knowledge of the factors leading to the development of such disease are not clearly defined. The National Institute of Neurological Disease and Blindness has recognized that clinical research in cerebrovascular disease is seriously hampered by a shortage of research facilities, including personnel, available beds, outpatient facilities, and patient population for acute and long-term study. The VA has also recognized that improved patient care requires the development and evaluation of additional diagnostic and therapeutic clinical methodology.

The VA, with its well documented medical histories, coupled with the size of the veteran population, the age of the veteran, and the likelihood of an increasing number of veteran patients being hospitalized with strokes, offers an excellent opportunity for conjoined research into the field of cerebral vascular disease by certain VA hospitals and affiliated university medical programs receiving National Institute of Health-National Institute of Neurological Diseases and Blindness support. There is need to define the area of therapy required subsequent to an occlusion of an artery resulting in a certain amount of brain destruction. There is need to obtain results that can be measured. There is a need to learn about the blood vessels, their pathology, their chemistry, and the clinical syndromes resulting from their obstruction. Exploratory pilot ventures have been initiated by the VA to work out the technical and administrative details leading to the establishment of stroke centers specializing in various aspects of cerebral vascular disease.

Research Centers are envisioned in which the major stress will be on finding the causative factors for the development of changes in blood vessels that lead to strokes; centers where studies into new methods for the rehabilitation of the stroke disabled patient will be carried out; centers where the major emphasis will be on the study and treatment of the language mechanism disturbances (aphasia) of stroke patients; and centers where the correlation of minor or major changes in the brain, due to occlusive disease of the blood vessels, is fully studied. At other centers the stress will be on finding new methods for the early diagnosis of impending stroke and for the fuller evaluation of completed strokes.

In about two weeks our PM&R Research Study Group is scheduled to meet again in VA Central Office to discuss and embelish a proposed pilot study concerning certain aspects of rehabilitation of hemiplegia caused by cerebral vascular accident. From this pilot we plan to go to a full blown cooperative study involving many Veterans Administration Hospitals. A study of even this magnitude will yield only a few answers to our many questions concerning this disability. Yet, we are certain that, in the long run, the results will be worthy of our best efforts and will be an acceptable contribution to the fund of knowledge concerning stroke and hemiplegia.

Summary

The prime cause of hemiplegia, the most crippling disability among Americans,

is cerebral vascular accident - or stroke. About two million of this country's people have had one or more strokes and there are now about three-quarter million new victims each year.

Medical advances during the past several decades haves so preserved and extended life that we are now seeing more stroke cases than heretofore but this increase is chiefly in the seventh decade and older age group.

Over an eight year period, the number of C. V. A. patients treated in Veterans Administration Hospitals, who were 65 or older went up 23% over the total number of those less than this age, from 1957 to 1964. During the same period the over-all mortality rate decreased from 29.5% to 23.2%.

We look to research for better understanding of the causes of stroke together with methods of prevention, medical treatment and rehabilitation of resultant hemiplegia.

EDITORIAL

PHYSIATRY AND THE PHYSICIAN

The doctor has a basic responsibility to return his patients to society in the best possible state of health. When this is not feasible because of disability, he consults with the physiatrist to retrain his patients to live and to work with what is left. The science of medicine that prepares the disabled person to take his place in society with the most favorable prognosis is known as Physical Medicine and Rehabilitation or Physiatry. It is also that art of medicine that combines the efforts of all medical and surgical specialties with paramedical programs to evaluate the handicapped most completely and to treat them most effectively.

Rehabilitation is not the sole responsibility of the physiatrist according to the concepts of Dr. Howard A. Rusk (1). *If the internist, the neurologist, the orthopedic surgeon, or any other specialist sincerely understands and has the personality to motivate the disabled, has the necessary skills, specific training and the time to work uninterruptedly with the handicapped, he is as capable as any physiatrist to direct this program. Rehabilitation is a full-time job, and this responsibility must not be delegated to personnel that solve only a single part of the problem. It is precisely this factor that is usually at fault when the patient fails to reach his rehabilitation goal.*

Who are the individuals that make up the rehabilitation evaluation and treatment team? By far the most important person is the patient himself. He must be physically and mentally able to establish rapport with and enter into training programs with the different members. Next, are the various specialists in medicine and surgery treating the patient's pathology. Rush (2) *states, "Any program of rehabilitation is only as sound as the basic medical service of which it is a part. The diagnosis and prognosis must be accurate, for it is upon them that the feasibility of retraining is determined."*

Paramedical personnel play important roles in evaluating and treating the patient. The psychologist uses a battery of psychometric tests to investigate the mind, analyze the intelligence, determine vocational aptitudes, as well as uncover any irregular mental phenomena. The speech therapist and audiologist diagnose speech and hearing defects and, when feasible, offer training to overcome them. The prosthetist and orthotist prepare prostheses, splints, corsets and shoe modifications for the amputated, paralyzed and orthopedically disabled patients. The social worker investigates the social and economic problems that confront the patient and his family and provides for their management.

Physical restauration is the realm of the physical, occupational and corrective therapists. Physical therapy makes use of physical modalities, such as electricity, light, masage, manipulation and exercise to treat disease. Physical Medicine originated fifty years ago with the exclusive use of physical agents to treat disease by some physicians. Although this therapy is a strong link in the chain of physical medicine and rehabilitation, it is only one of the many components in the present-day practice of physiatry.

The large number of heavy, paralyzed patients curtailed the work of the female physical therapist, so strong, male corrective therapists have been recruited to lift these patients and supervise their exercise programs. Occupational therapy provides a program of mobilizing and strengthening joints and muscles utilizing arts and crafts. In the larger rehabilitation centers this discipline has been directed towards functional evaluation of the activities of daily living and training of the disabled homemaker in order to make the severely handicapped person self sufficient. The rehabilitation nurse also participates by teaching self-care activities in personal hygiene, eating and ambulation in the hospital ward in addition to routine nursing duties. For many of the more severely disabled individuals, training them to become self-sufficient is the only rehabilitation goal.

Vocational guidance, training and placement in a productive job is considered the final achievement of rehabilitation. For those patients who have long-term, chronic illnesses, manual arts therapists can train them in an industrial profession, and the educational therapist can teach them commercial courses or regular school subjects while they are hospitalized. With this preparation many have acquired sufficient scholastic credit to graduate from high school and even college. It is the duty of the vocational counselor to match the abilities of the patient with the requirements of the job and place him into training for lucrative employment.

This, in brief, is the modern concept of total medical care of the disabled patient. For best results this service should be provided in a rehabilitation center complete with all the necessary personnel and equipment.

* * * *

From April 25to May 6, 1966 the Section of Physical Medicine and Rehabilitation of the Puerto Rico Medical Association in collaboration with the University of Puerto Rico School of Medicine sponsored the First Caribbean

Congress in Physical Medicine and Rehabilitation at San Juan, Puerto Rico. Seminars on Arthritis and Rheumatism, The Stroke Patient, Electrodiagnosis of Neuromuscular Diseases, The Scope of Physical Medicine and Rehabilitation, and Rehabilitation of the Amputee were held at the Hotel El San Juan, April 25 to 29, 1966. The prosthetic team of the University of California at Los Angeles presented a short course on Prostheses for Upper and Lower Extremity Amputees at the Rehabilitation Center of the Puerto Rico Medical Center during May 2 to 6, 1966. A total of 387 registered, including 186 physicians. Forty doctors from Latin America and the Caribbean countries attended. Sixty-six papers were presented in addition to a great deal of practical and informative discussion by many experts in the audience.

The Editorial Board has selected a few of the many outstanding scientific contributions for publication in this issue of the Boletin. *All of the papers will be published in the Proceedings of the First Caribbean Congress in Physical Medicine and Rehabilitation, which will be sent to the registrants. Additional copies will be made available to interested individuals upon request in writing to the Puerto Rico Medical Association.*

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NOTICIAS

Locales

Sintonice nuestro programa televisado "Divulgación Médica" por la nueva estación WITA — Canal 30, todos los sábados de 5:00 a 5:30 P. M., comenzando el sábado 25 de junio de 1966.

Junio 11 al 17 de julio — Semana del Médico Interno y Residente.

Julio 15 de 1966 , 8:00 P.M. — Agape a Internos y Residentes en el Club de la Asociación Médica. En esta actividad además de proveerles un rato de entretenimiento se ofrecerán regalos, los cuales serán rifados entre los asistentes. Entre los regalos se incluirá una mquina de lavar marca Philco valorada en $325.00 cortesía de la SSS y de Saji Discount de Santurce.

CONVENCION SEMIANUAL

Julio 31 de 1966, 10:30 A.M. — Convención Semianual del Distrito Este, en el Holiday Inn. Se celebrará un panel ese día sobre hipertensión; habrá coctel y buffet.

Nov. 15-19

Asamblea Anual de la Asociación Médica de Puerto Rico, Hotel San Juan.

Nacionales

NLN PROMOTES GRADUATE EDUCATION IN NURSING

"Masters Education: Route to Opportunities in Modern Nursing" is the title of a new education and career guidance publication issued recently by the National League for Nursing, New York.

It provides general information about sources of financial assistance for the pursuit of graduate education in nursing, and lists, with detailed information about each, the colleges and universities offering masters programs accredited by the National League for Nursing.

Prepared by the NLN Department of Baccalaureate and Higher Degree Programs, "Masters Education: Route to Opportunities in Modern Nursing" is a companion piece to the department's booklet, "College Education: Key to a Professional Career in Nursing." The latter, now available in a 1966 edition, is addressed to prospective students, registered nurses, and nursing students who wish initial senior college preparation in nursing.

Both publications are available from the National League for Nursing, 10 Columbus Circle, New York, New York 10019, at 25c. for single copies, with a 20% discount on orders for 10 or more copies.

STUDY OF DRUG PURCHASE PROBLEMS AND POLICIES

A "Study of Drug Purchase Problems and Policies" was released today by the Welfare Administration, U. S. Department of Health, Education, and Welfare.

The publication is a 91 — page review of programs and policies of American and foreign organizations that involve the purchase of large quantities of drugs. It was prepared by Raymond Clapp, a consultant to the Welfare Administration's Research Division. The data provide resource material for State public health and welfare agencies concerned with the operation of the new Medical Assistance Program for public assistance recipients and other low income persons which was authorized by the 1965 amendments to the Social Security Act (Title XIX).

The publication points out that nursing's most critical need today is for qualified teachers, clinical specialists, supervisors and administrators — positions for which graduate preparation is required.

Drugs sold on physicians prescriptions account for the greatest increase in drug prices since 1939, the study notes, and consequently most of the contents of the report deal with methods of enabling physicians to prescribe economically without sacrificing the quality or efficacy of the drugs their patients receive.

Since more than 15,000 prescription drugs are now in common use and since any one of them may be sold under as many as 50 to 75 trade names, physicians need simplified methods of selecting those they prescribe.

Methods used by the Hometown Medical Care Program of the Veterans Administration, the Department of Defense, and various State programs of vendor payments for drugs used by public assistance recipients are described as are the methods of the General Medical Service of Scotland and the National Health Service of England and Wales. Other programs described include the pre-payment drug plan of the Group Health Cooperative of Puget Sound, Seattle, and the drug purchase program operated jointly by the American Association of Retired Persons and the National Retired Teachers Association which sells both generic and brand name drugs to some 7 million persons on a non-profit basis.

Major recommendation contained in the report is for the employment of a consultant in drug economics on the staff of the Federal agency and similar consultants on the staffs of State public welfare departments. These consultants would work with medical and pharmaceutical committees in preparing guidelines for physicians and pharmacists, would identify high cost drugs most frequently used in the Medical Assistance Program for which there are lower cost counterparts, and would devise methods for assesing physicians' drug prescription practices.

With the increasing use of electronic data processing in public welfare agencies, better data to help the physician evaluate his prescription practices is becoming available, the report notes.

Copies can be purchased from the Superintendent of Documents, U. S. Government Printing Office, Washington, D.C. 20402, at 55 cents.

BIRTH IN PUERTO RICO AND THE VIRGIN ISLANDS

Levels and Trends

In 1963, as in the past, birth rates in Puerto Rico and the Virgin Islands were higher than that of the United States. Puerto Rico's birth rate of 30.6 per 1,000 population was 41 percent higher than the rate of 21.7 for the United States, and the Virgin Islands' rate of 38.1 was 76 percent above that for the United States. Only one State, Alaska, had a higher birth rate than Puerto Rico (31.0, compared with 30.6), and no State had a higher rate than the Virgin Islands.

Assuming that the 1963 birth and death rates were to prevail indefinitely and that the respective areas were closed to in- and out—migration, the population of the United States would double in 46 years, Puerto Rico in 33 years, and the Virgin Islands in 26 years. Such rates, although hypothetical, emphasize the different potentials for population growth offered by current birth and death rates in these areas.

Birth rates in the United States are below those in Puerto Rico, in part, because of differences in the age-sex compositions of the respective populations. Adjusting for these differences, using the 1963

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** Based on female age-specific birth-rate estimates prepared by Puerto Rico Department of Health, Division of Demographic Registry and Vital Statistics, and shown in table 11 of Annual Vital Statistics Report, 1963. The 1963 age-sex adjusted rate for Puerto Rico is 26.4 births per 1,000 population.*

age distribution of women in the United States as a standard, yields an age-sex-standardized birth rate for Puerto Rico that is only 22 percent above the birth rate of the United States.* In other words, about half of the 41-percent difference between the unadjusted birth rates of Puerto Rico and the United States is due to differences in age-sex composition. The remainder of the difference is due to higher age-specific birth rates in Puerto Rico.

Trends in the birth rate, which are shown in table 15, have not been the same for Puerto Rico and the Virgin Islands as for the United States. In Puerto Rico, the birth rate reached a postwar peak of 42.2 in 1947 and has declined fairly steadily since then. In the Virgin Islands, however, the 1962 birth rate of 39.4 was the highest observed in the postwar period. The lowest postwar rate, 30.7, was recorded in 1948. In general, there has been an upward trend in the birth rate in the Virgin Islands, but it has been irregular. Part of this irregularity may be due to random variations associated with small numbers of births (800 to 1,500 in the postwar period).

Health Characteristics of the Newborn Infant

Health indexes of the newborn infant in Puerto Rico and the Virgin Islands were at measureably lower levels in 1963 than in the United States. The percentage of births delivered in hospitals was 84.9 in Puerto Rico and 87.7 in the Virgin Islands compared with 97.4 in the United States. Since hospitals are concentrated in urban areas, the percent of in-hospital births is associated with the degree to which a population is urbanized, which is also highest in the United States. The percentages of in-hospital births to residents of metropolitan areas in Puerto Rico and to urban residents in the Virgin Islands are closer to those of comparable populations in the United States as shown below.

Residence	United States	Puerto Rico	Virgin Islands
	Percent of births in hospitals		
Total-	97.4	84.9	87.7
SMSA	98.9	91.5	—
Urban	98.4	—	[1]98.9

Puerto Rico and the Virgin Islands show higher percentages of immature births than does the United States. The percent of live births weighing 2,500 grams or less was 8.2 in the United States, 8.9 in the Virgin Islands, and 9.8 in Puerto Rico in 1963.

There is some evidence that immaturity is more frequent in the lower socioeconomic classes of Puerto Rico. This is shown by the percentage of immature births in 1962, according to the education of the father. (This tabulation is not available for 1963.)

[1] *Includes only the city of Charlotte Amalie (St. Thomas Island), Virgin Islands.*

Internacionales

PRIMER CONGRESO DE LA ASOCIACION LATINO AMERICANA DE SOCIEDADES DE BIOLOGIA Y MEDICINA NUCLEAR

El Primer Congreso de la Asociación Latino Americana de Sociedades de Biología y Medicina

Nuclear, se realizará en Lima, Perú del 2 al 8 de octubre del presente año; correspondiendo su organización a la Sociedad Peruana de Biología y Medicina Nuclear.

El programa tentativo comprende los siguientes temas oficiales: a) Isótopos Radioactivos en Endocrinología, b) Isótopos Radioactivos en Hematología y c) Isótopos Radioactívos en Nefrología. Habrá además una sección de temas libres y se organizará Mesas Redondas sobre tópicos de actualidad.

Durante los días del Congreso se realizará la Asamblea General de la Asociación Latino Americana de Sociedades de Biología y Medicina Nuclear. De otro lado, se programará un viaje al Cuzco para realizar visitas culturales a los lugares incaicos, incluyendo Machu-Picchu.

Instrucciones para los Autores:

El Boletín acepta para su publicación artículos relativos a medicina y cirugía y las ciencias afines. Igualmente acepta artículos especiales y correspondencia que pudiera ser de interés general para la profesión médica.

El artículo, si se aceptara, será con la condición de que se publicará únicamente en esta revista.

Para facilitar la labor de revisión de la Junta Editora y del impresor, se requiere de los autores que sigan las siguientes instrucciones:

a) Los trabajos deberán estar escritos a máquina a doble espacio y por un solo lado de cada página, en duplicado y con amplio margen.

b) En página separada debe incluirse lo siguiente: título (no excediendo de 80 letras y espacios), nombre del autor (es), institución y dirección postal del autor.

c) Artículos referentes a resultados de estudios clínicos o investigaciones de laboratorio deben organizarse bajo los siguientes encabezamientos: (1) introducción, (2) material y métodos, (3) resultados, (4) discusión, (5) resumen (en español e inglés), y (6) referencias.

d) Artículos referentes a estudios de casos aislados deben organizarse en la siguiente forma: (1) introducción, (2) observaciones del caso, (3) discusión, (4) resumen (en español e inglés), (5) referencias.

è) Las tablas, notas al calce y leyendas deben aparecer en hojas separadas.

f) Si un artículo ha sido leído en alguna reunión o congreso, así debe hacerse constar como una nota al calce.

g) Deben usarse los nombres genéricos de los medicamentos. Podrán usarse también los nombres comerciales, entre paréntesis, si así se desea.

h) Se usará con preferencia el sistema métrico de pesos y medidas.

i) Las fotografías y microfotografías se someterán como copias en papel de lustre sin montar. Los dibujos y gráficas deben prepararse a tinta negra y en papel blanco. Todas las ilustraciones deben estar numeradas (números arábigos) e indicar la parte superior de las mismas. Debe escribirse una leyenda para cada ilustración.

j) Las referencias deben ser numeradas sucesivamente de acuerdo con su aparición en el texto. Los siguientes ejemplos pueden servir de modelo:

6. *Koppisch, E.* Pathology of arteriosclerosis. Bol. Asoc. Med. P. Rico 46: 505, 1954. (artículo de revista).
4. *Wintrobe, M. M.* Clinical Hematology, 3rd Ed. Lea and Febiger, Philadelphia, 1952, p. 67. (libro).

Deben usarse solamente las abreviaturas indicadas en el Cumulative Index Medicus que publica la Asociación Médica Americana.

Instructions to Authors:

The Boletín will accept for publication contributions relating to the various areas of medicine surgery and allied medical sciences. Special articles and correspondence on subjects of general interest to physicians will also be accepted. All material is accepted with the understanding that it is to be published solely in this journal.

In order to facilitate review of the article by the Editorial Board and the work of the printer, the authors must conform with the following instructions:

a) The entire manuscript, including legends and references, should be typewritten double-spaced in duplicate with ample margins.

b) A separate title page should include the following: title (not to exceed 80 characters and spaces), author's name (s); institution, and author's mailing address.

c) Articles reporting the results of clinical studies or laboratory investigation should be

organized under the following headings: (1) introduction, (2) material and methods, (3) results, (4) discussion, (5) summary in English and Spanish, (6) references.

d) Case reports will include (1) introduction, (2) description of the case, (3) discussion, (4) summary in English and Spanish, (5) references.

e) Tables, footnotes and legends to figures should appear in separate sheets.

f) If the paper has been presented at a meeting, the place and date should be stated as a footnote.

g) Generic names of drugs should be used. Trade names may also be given in parenthesis, if desired.

h) Metric units of measurement should be used preferentially.

i) Photographs and photomicrographs should be submitted as glossy prints, unmounted. Drawings and graphs should be made in black ink on white paper. All illustrations should be numbered (Arabic) and the top indicated. A legend should be given for each.

j) References should be numbered serially as they appear in the text. The following form will be used:

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4. *Wintrobe, M. M.* Clinical Hematology, 3rd Ed. Lea and Febiger, Philadelphia, 1952, p. 67, (for books).

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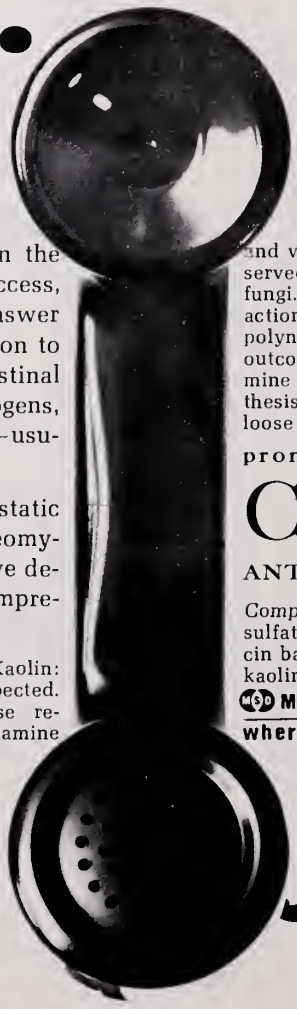


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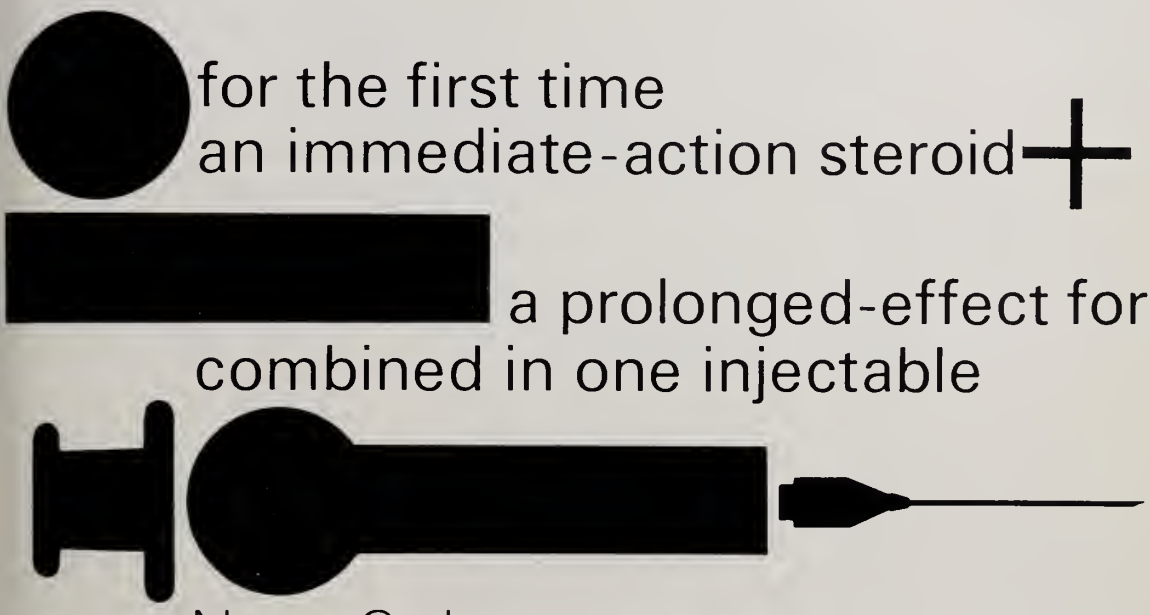
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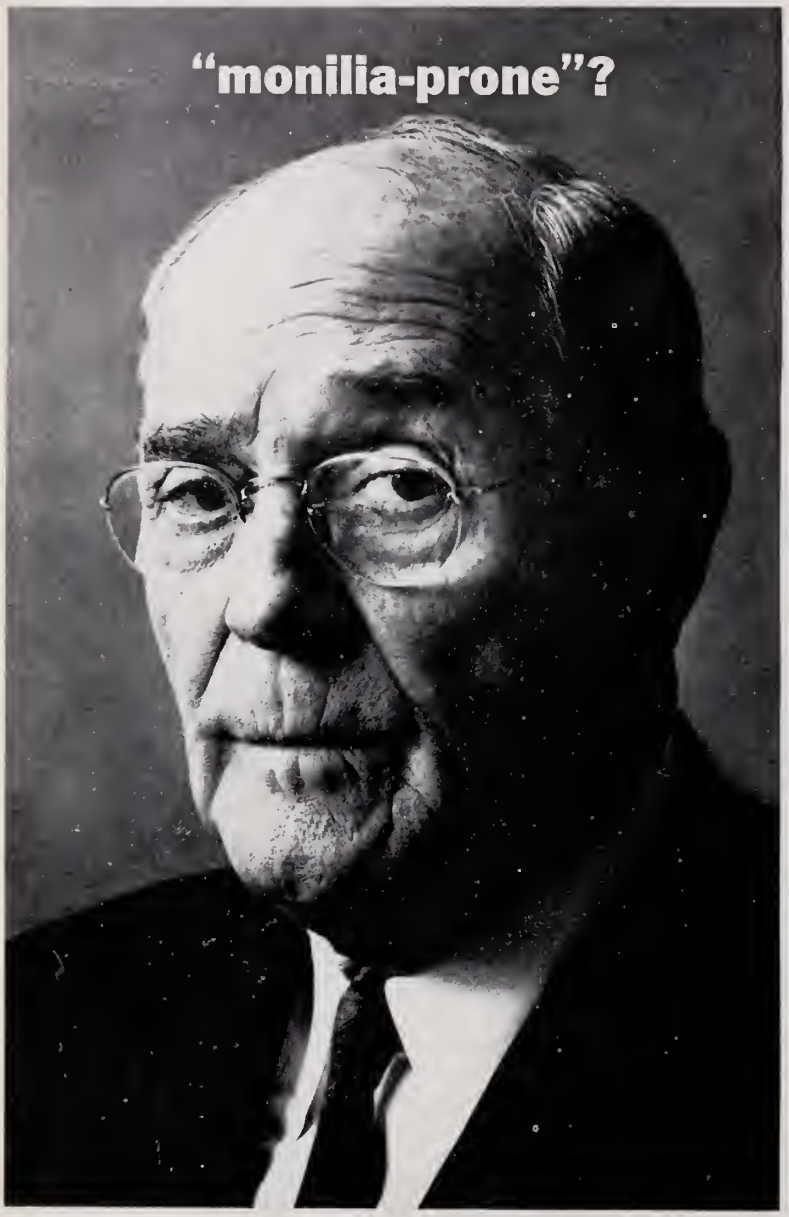
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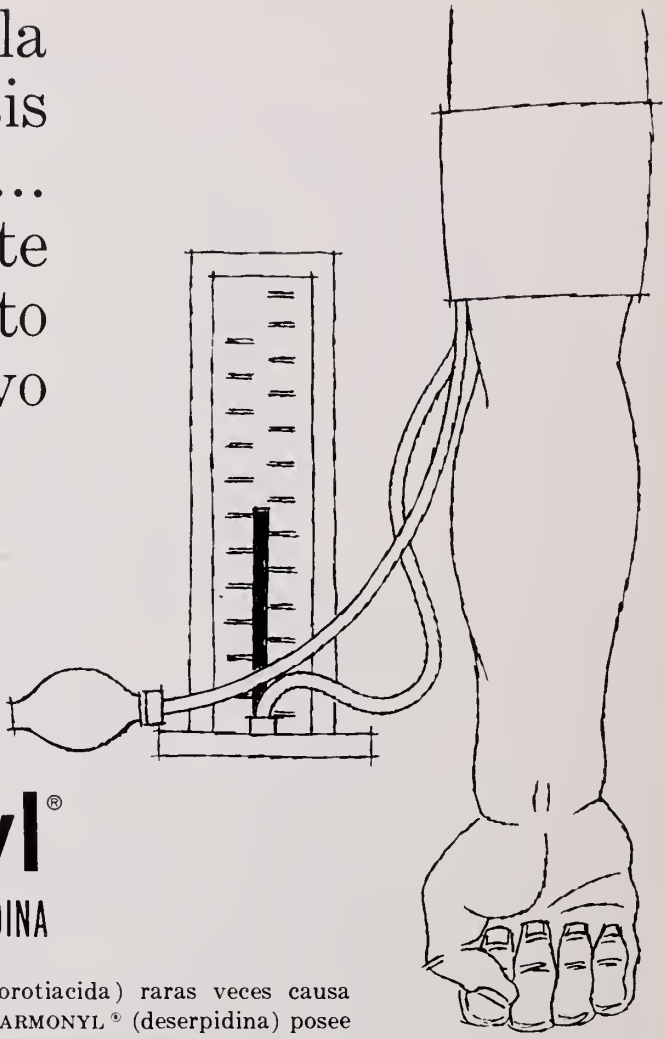
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A REVIEW

DIAGNOSIS OF DIGITALIS INTOXICATION

José M. Torres Gómez, M. D., F.A.C.P.

Notwithstanding the great advances made in the treatment of cardiac diseases, Withering's digitalis remains, perhaps, as the most useful drug, and according to many, as the most valuable in the control of myocardial failure. The incidence of heart disease is increasing everywhere and, in the same proportion, so will the use of digitalis. New aspects in the treatment of heart disease, like cardiac surgery during extra-corporeal circulation, are influencing the development of intensive investigation of the drug so that it may be used to its maximum. It is obvious, therefore, that the knowledge of the proper use of digitalis is getting to be more important and more necessary for the practicing physician. It becomes doubly so when complications appear as toxic plasma levels are reached. In order to prevent them, we must be familiar with what is meant by the ineffective, therapeutic, toxic, and lethal zones of the drug.

Figure 1 is a graphic presentation of the different effects of digitalis at different concentrations as it accumulates in the blood. You will notice a rather large ineffective zone. In other words, you need to give about 80% of the total digitalizing amount just to enter the therapeutic zone; that is, just to obtain a therapeutic effect. It seems as if the action of digitalis is an "all or nothing" phenomenon (1). With other potent drugs you can double or even

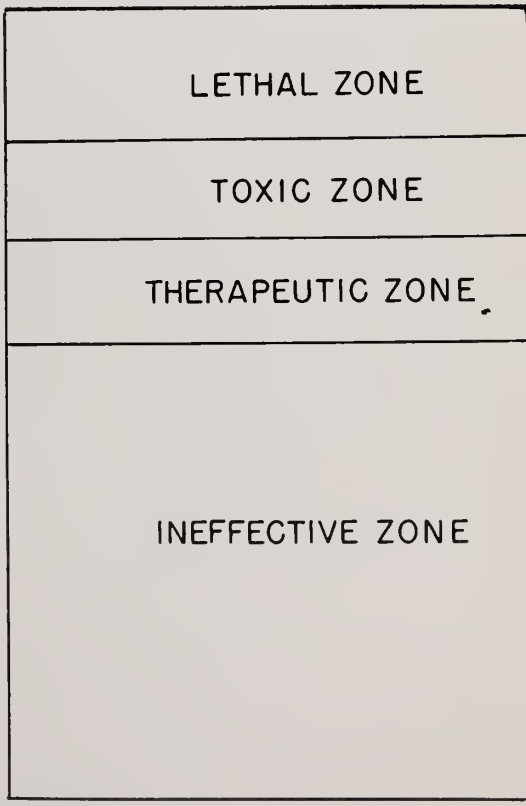


Fig. 1: Levels of digitalis effect. Reproduced from Selzer (1).

triple the therapeutic dose without getting into serious difficulties, but with digitalis you can not. You will produce intoxication in over 50% of the cases by just doubling the therapeutic dose, as the range between those two is very narrow (2).

The toxic zone can be entered *rapidly* by overestimating the initial dose, or *slowly*, by too large maintenance doses. On the other hand, a small initial dose may not reach the therapeutic zone, or if reached, small maintenance doses lead to loss of digitalis effect as the ineffective zone is re-entered.

This applies to *all* digitalis preparations although the duration of the effect varies with different glycosides according to their dissipation rates, i.e., the effect of those that are excreted and/or destroyed slowly will last longer, and vice-versa. Besides, as therapeutic and toxic levels vary with each individual, standard digitalizing doses should be applied only as guides to each patient's need since with them, the toxic level will be reached in a given number of cases. We must be especially cautious with those patients in whom we have to produce the earliest signs of toxicity in order to be sure that we have obtained the maximum therapeutic effect. In these cases it is very important not only to know but to recognize toxic manifestations as soon as possible so that we may avoid reaching more dangerous levels.

Manifestations of Toxicity

The list presented, though apparently very comprehensive, does not include all the manifestations reported in the literature. For instance, in the neurological group, Batterman once reported mandibular pains, leg pains, and a host of other sensations that, due to their rarity and lack of specificity, are not worth while listing (3).

TABLE I: MANIFESTATION OF DIGITALIS TOXICITY

1) Gastro-intestinal
a) Nausea and/or vomiting
b) Anorexia
c) Abdominal cramps
d) Diarrhea
2) Neurological
a) Visual changes
Dimness and/or blurring
Scotomata
Green and/or yellow flashes
b) Headache
c) Mental disturbances
Restlessness; Vertigo
Increased irritability
Lethargy; Somnolence
Disorientation; Delirium
3) Cardiac: Clinical and EKG
4) Idiosyncracy (?)

It has been estimated that as high as 20% of those receiving digitalis develop toxicity at some time during the course of treatment (4). It has also been claimed that certain digitalis preparations tend to produce qualitative differences in the signs of intoxication. Contrary to this, Marriott states that in a series of patients deliberately made toxic, different oral glycosides did *not* produce specific patterns of toxicity. Even patients rendered toxic on repeated occasions with the same glycoside, exhibited different toxic syndromes (5).

Perhaps the commonest signs are nausea and vomiting with premature ventricular contractions (PVCs) (bigeminy) running

a close third. Actually, anorexia may precede all other symptoms, but its development is so subtle that often this symptom is missed even by the patient, unless it is sought for on direct questioning. This is especially true in the elderly.

Gastric symptoms are as a rule of central origin whether due to direct stimulation of the vomiting center in the medulla or to reflex action from the heart. Symptoms due to local gastric irritation may happen occasionally with digitalis leaf. Diarrhea and abdominal cramps are very rare; diarrhea is seen mostly when unusually high doses are used.

We must be on the look-out for neurological symptoms in the aged for they can be erroneously concidered to be arteriosclerotic manifestations. One must have a high index of suspicion in those who develop personality changes, depression, loss of memory, and even delirium. Church and Marriott described three cases that exhibited the latter (6).

Arrhythmias are specified in the cardiac manifestations because all of them can result from digitalis intoxication. However, the following comments are in order: 1) Between 80 and 95% of patients with severe digitalis toxicity develop arrhythmias (7, 8). 2). Multifocal PVCs, A-V dissociation, and ventricular tachycardia constitute over 90% of then (9). 3). When paroxysmal atrial tachycardia (PAT) occurs with block in an individual taking digitalis, the probabilities are that it is due to toxicity from the drug (10). 4). Atrial flutter is rarely seen as a manifestation of digitalis toxicity (11).

Sagging of the ST segment and inversion of the T waves are EKG signs of digitalis effect but not of toxicity. However, when the QT interval shortens considerably, when marked bradycardia ensues, and when PR and QRS durations are delayed so that blocks appear, the presence of digitalis toxicity must be accepted.

Myocardial damage and congestive heart failure secondary to digitalis intoxication have been reported. Studies carried out in intoxicated cats and dogs have revealed the presence of hemorrhages and necrosis in the subendocardial layers and papillary muscle. In humans, mild intracellular edema and slight increase in the number of interstitial cells have been found in autopsy material. However, this finding has not been accepted as related specifically to digitalis poisoning (12).

In children, the situation is somewhat different. Anorexia, nausea and vomiting are seldom conspicuous. Probably the only reliable guide is the EKG. Usual premonitory signs are slowing of the heart rate and prolongation of the PR interval. The commonest abnormalities observed are S-A node depression, ectopic supra-ventricular beats and rhythm, and A-V conduction disturbances. Frequent EKGs are needed during the digitalization of premature and newborn infants since they are more susceptible to digitalis intoxication than older infants (13).

Idiosyncracy to digitalis is very rare. When symptoms and signs occur that might suggest its presence, the probabilities are that the patient is simply intoxicated.

Etiology

The principal cause of digitalis intoxication is overdosage. This can be classified as

absolute, moderate, or relative. By absolute is meant a grossly high dose. This may come as a result of repeated increases in attempts to correct intractable heart failure, gross errors by the patient in taking digitalis or by the nurse in giving it, or by giving it too rapidly.

TABLE II: ETIOLOGY OF DIGITALIS INTOXICATION *

A) Overdose of digitalis
1) Absolute (grossly high)
a) Increased in an attempt to correct intractable heart failure
b) Gross error by patient or nurse
c) Error in timing (too much digitalis too rapidly given)
2) Moderate (above maximum recommended)
d) Use of pulse rate as criteria of dosage in absence of atrial fibrillation or flutter
3) Relative (normal; excessive for patient)
e) Relatively high maintenance dosage in effort to control intractable CHF
f) Failure to follow patients (readjust dose) with CHF during long term treatment
g) Failure to lower maintenace during limiting circumstances (oliguria, etc)
B) Poor myocardial status
C) Electrolyte imbalance
1) Potassium deficit due to:
a) Diuresis
b) IV hypertonic saline or dextrose
c) Diarrhea
2) Calcium therapy

* Modified after Shrager (8)

By a moderate overdose is meant one that is just above the maximum recommended dose. The difficulties produced in this case are usually not serious. Reliance on the pulse rate as a criterium of dosage in the absence of atrial fibrillation or flutter was responsible for this degree of toxicity in the experience of Shrager (8). We must be cautious when anemic patients are digitalized, or those with cor pulmonale, hyperthyroidism, constrictive pericarditis, or mitral stenosis in the presence of sinus rhythm, since the pulse may remain relatively rapid in these cases in spite of their being adequately digitalized. Attempts to lower the pulse rate through further increases in digitalis dosage will frequently produce intoxication.

By relative overdosage is meant a dose that, though normal by accepted standards, is excessive for the patient in question. Not only is there need for individualizing digitalization dosages but there is also need for evaluating the patient who has been on a maintenance dose during long-term treatment. Digitalis intoxication is not infrequent in patients who receive maintenance doses corresponding to 0.2 mg of digitoxin daily. On the other hand, it has been my experience, that patients who develop cardiac failure after having received a daily maintenance dose corresponding to 0.1 mg. of digitoxin for more than 4 months, the probabilities are that they have developed decompensation because of lack of digitalis rather than because of excess of it.

In regard to digoxin, I have observed that a number of cases become toxic when the recommended digitalization dose of 2.5 mg is used. I have avoided intoxication and have been able to adequately digitalize most of my patients with this glycoside by only using 1.5 mg in 24 hours.

There are also certain limiting conditions or predisposing factors which make it imperative to reduce the dose, or even to stop the drug, as under such circumstances, patients become intoxicated even though they may be receiving small doses.

Factors That May Increase Digitalis Sensitivity

Perhaps the commonest accepted predisposing factor at the present time is *hypopotassemia*. It has been shown that when the serum potassium level is low, an ordinarily non-toxic amount of digitalis may be sufficient to cause symptoms and signs of overdosage which disappear when potassium salts are administered. Both experimental and clinical evidence show that an increased serum potassium concentration counteracts and that hypokalemia accentuates the effects of the cardiac glycosides (14).

TABLE III: FACTORS THAT MAY INCREASE DIGITALIS SENSITIVITY

1) Advanced age
2) Severe heart disease
3) Severe congestive heart failure
4) Preceding diuresis
5) Renal insufficiency
6) Diarrhea
7) Vomiting or gastric intubation
8) Calcium administration
9) Hypothyroidism
10) Etiology of heart disease (?)
11) Type of digitalis glycoside (?)

Paradoxically enough, the word potassium does not appear in table III, but it is implicated all throughout, for potassium depletion is encountered as a result of malnutrition, diarrhea, gastric intubation, diuretic therapy, steroid therapy, hemodialysis for uremia, etc. Caution is particularly indicated in the patient who comes in severe congestive heart failure as when you treat this patient with full digitalizing doses and potent diuretics concommitantly, potassium stores may be acutely depleted and digitalis intoxication occurs. *Rapid* digitalization should also be avoided in these patients for the same reason.

Advanced age also makes an individual, as a rule, unduly sensitive to digitalis. Not infrequently we come across a 65 or 70 year old patient whose maintenance dose has to be reduced from daily to only three times a week because the minimum daily dose now causes intoxication. Whether this is due to potassium depletion, to a reduced number of normal cardiac muscle fibers, or to the presence of early renal insufficiency, is pure speculation.

Severe heart disease is another limiting condition. One cannot say that the amount of digitalis needed by a patient is a measure of the degree of his heart disease. Too many factors are involved. However, in general, the therapeutic range of digitalis tends to narrow as the heart disease progresses. Increased requirements of digitalis gradually near the toxic dose until a point is finally reached where the toxic dose is lower than the therapeutic one, and the patient develops digitalis intoxication before cardiac compensation is achieved.

Increased sensitivity to digitalis is also observed in *renal failure* because digitalis is retained in patients with renal insufficiency. This has been recently confirmed in studies performed with tritiated digoxin. In normals, 80% of the digitalizing dose is excreted in the urine and about 12% in the stools, for a total of 92%, within a period of a week. In renal failure, although stool excretion increases from 12 to 17%, renal excretion diminishes to 25%, for a total of only 42% (15). Therefore, if you continue to give a standard maintenance

dose to these patients their serum concentration will gradually increase and you will intoxicate them. Beware of peritoneal dialysis in these cases because, though you may remove significant quantities of potassium, the amount of digitalis removed is minimal, and the probabilities of developing intoxication are then increased.

Studies with tritiated digoxin have also revealed why *hypothyroid* patients are toxicity prone. A dose of 1mg. was given intravenously to hyper, hypo-, and euthyroid patients. Not only higher blood levels were demonstrated in the hypothyroid cases but also their digoxin excretion in the urine and in the stools was low (16).

Much has been written about the so-called synergistic action of digitalis and *calcium*. Sudden death has been reported in digitalized cases where calcium was used intravenously. Though the exact mechanism of action is not known with certainty, it is probably safest not to use calcium in the individual who is receiving digitalis. The antagonism that exists between the effects of calcium and potassium on the heart may be implicated in the fatal outcome, since digitalis tends to displace potassium from the muscle cell.

Recent studies have been performed with total body perfusion techniques for open heart surgery to find out whether the concentration of digitalis is reduced in the tissues of the patient as a result of *extracorporeal circulation*. Atrial muscle biopsies taken before and after carrying out the bypass did not reveal any significant reduction. However, other studies carried out in infants and dogs revealed decreased tolerance to digitalis administered one hour after perfusion. In 80% of animals tested this decreased tolerance remained for four hours, and in 40% of animals for seven hours, after perfusion. The question that these studies bring up is whether digitalis should be given to patients undergoing this type of surgery, and if so, how much and when. At least, no difference in the incidence of arrhythmias has been observed during surgery among patients who have and who have not received digitalis (17).

An interesting recent observation has been the appearance of manifestation of toxicity in digitalized patients after conversion with direct current *countershock*. Patients with atrial fibrillation who had not manifested any signs of toxicity though adequately digitalized, developed blocks, PVCs, bradycardias, nodal rhythm, and fatal ventricular fibrillation upon conversion. Even a group of patients who did not convert showed manifestations of digitalis intoxication after receiving the shock (18). It appears that direct current counter-shock conversion may be hazardous in digitalized patients. Does it potentiate the toxic action of digitalis? At any rate, it may be wiser to stop digitalis several days prior to the application of countershock.

Diagnostic Tests

There are occasions when the diagnosis of digitalis intoxication is in doubt. Shrager has proposed the criteria outlined in Table IV to be used as a guide in order to facilitate a diagnosis. He suggests that if Part A and any two conditions of Part B exist, the diagnosis of digitalis intoxication is in order (8).

Diagnostic tests for digitalis toxicity have been offered but they are still in the expe-

rimental stage. Among them, Tensilon R (edrophonium chloride) has been used. It enhances the effect of digitalis by inhibiting the action of acetylcholinesterase. If the

TABLE IV: CRITERIA OF DIGITALIS TOXICITY *

A) Must be taking 50% or more of the average recommended dose
B) Two or more of the following must also be present:
  1) Strong clinical suspicion to staff
  2) Return of signs and symptoms to normal after stopping or reducing digitalis, or after potassium therapy (in expected time)
  3) One of the following arrhythmias (EKG):
    a) P A T with block
    b) A-V dissociation (interference)
    c) Bigeminy or trigeminy
  4) Evidence of predisposing factor

* Modified after Shrager (8)

ectopic activity is due to digitalis intoxication, it will increase as Tensilon is administered. If it is not due to digitalis, it will remain unaffected (19). Though the action of Tensilon is very transient, the test has its dangers.

The use of citrate salts has also been offered as a test for digitalis toxicity. They bind the ionizable calcium in the blood forming a stable soluble complex that is later excreted in the urine. The serum calcium ion seems to alter the cell membrane permeability so that a blocking effect is created preventing potassium from entering the myocardial cell. By binding the calcium in the serum this blocking effect is lessened, potassium is then allowed to move inward, an the effects of digitalis intoxication are neutralized (20, 21).

The citrate salts apparently affect only the digitalis- induced and not the aconitine-produced arrhythmias. Therefore, termination of the arrhythmia by this means probably indicates the existence of digitalis intoxication (22).

Summary

A partial review of the recent literature on different aspects of digitalis intoxication is presented. A few personal experiences with the use of digitalis preparations are included. The difficulties in the early detection of digitalis toxicity are pointed out. The importance of prompt and correct diagnosis of intoxication is stressed.

Resumen

Se presenta un repaso de algunos datos de reciente publicación en la literatura médica sobre distintos aspectos de intoxicación por digital. Se añaden algunas experiencias personales sobre el uso de dicha droga. Se señalan las dificultades que entorpecen el diagnóstico temprano de intoxicación por digital. Se recalca la importancia del diagnóstico correcto y precoz de dicho estado tóxico.

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PREVENTION OF ACUTE RENAL FAILURE

Lt. Colonel Kevin G. Barry, MC.

Since the advent of the "Artificial Kidney" almost twenty years ago, a large intellectual and monetary effort has been expended to reduce the mortality rate associated with acute renal failure.[1] in Korea, use of hemodialysis effected a reduction from 94 to 68 per cent in post-traumatic cases.[2] Today, despite our efforts, the patient with established renal failure still has less than a fifty-fifty chance of survival.

The importance of prophylaxis is underscored by our continued inability to improve the mortality statistics for patients with established renal failure. The studies reported herein suggest we have at hand prophylactic methods which will reduce the occurrence of renal failure to a fraction of its current incidence.

It is our belief that most patients with acute irreversible renal failure have passed through a phase of reversible failure which can usually be prevented and treated by mannitol diuresis and judicious hydration (Fig. 1). Application of these principles for prophylaxis requires abandonment of traditional fluid restriction for the surgical patient and maintenance of urine flow in the range of 100 ml per hour for all patients in whom renal failure is a clinical threat. This presentation will be devoted to the studies leading to our conclusions and methods we have found effective for prevention of acute renal failure.

Reprinted from Herbert R. Hawthorne, M. D., Vascular Surgery, Springfield, Illinois, Charles C. Thomas, Publisher.

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Mannitol

Since mannitol holds a central position in our prophylactic approach to renal failure, a brief review of its properties is warranted.

Mannitol is the reduced form of the six-carbon sugar mannose (Fig. 2). It was introduced to the biologic sciences in the late 1930's. During World War II when the supply of inulin (classically used for the determination of glomerular filtration rate and extracellular fluid volume) was curtailed for logistic reasons, the kinetics of mannitol were intensively studied. It was found that mannitol, like inulin, was limited in its distribution to the extracellular space, freely filtered across the glomerulus into the lumen of the renal tubule and not reabsorbable from it. Mannitol, therefore, was found to be a satisfactory substitute for inulin in the measurement of extracellular fluid volume and glomerular filtration rate. Unlike inulin, mannitol is a

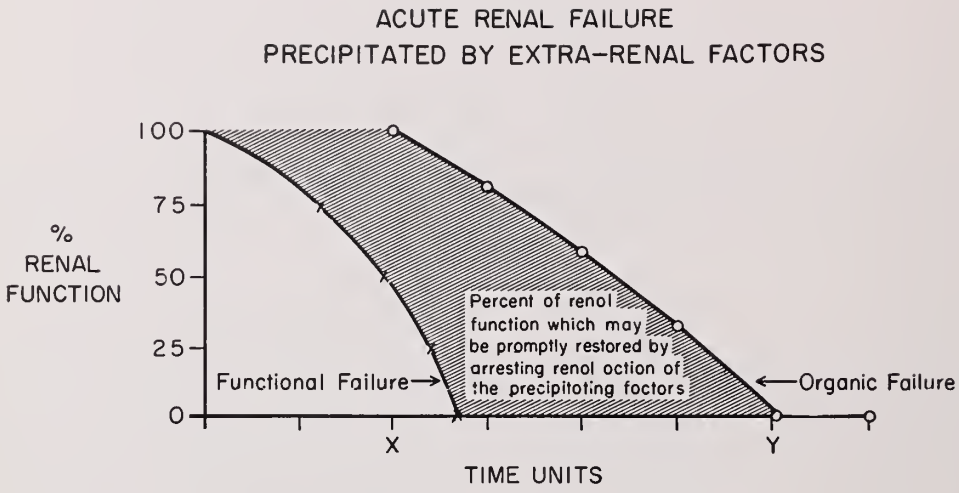


Fig. 1: Schematic representation of authors' concept of importance of time in the progression of functional to organic failure. Systemic hypotension may be used as an example of extrarenal precipitating factor. Reflex spasm of renal arteries occurs and renal blood flow is severely decreased. Glomerular filtration rate and urine flow fall rapidly. Finally, anuria occurs. If renal response to the hypotension is not arrested before time X, renal lesions are initiated. During the interval between time X and Y, therapy will be effective in alleviating functional component of failure and preventing further progression of organic lesions. At time Y, however, organic lesions are of such severity that total organic failure is present, pathologically characterized (in this example) by acute tubular necrosis. At this point, arresting renal effect of hypotension can have no immediate salutary effect since patient is suffering classical, organic renal shutdown.

MANNITOL PROPERTIES

CH_2OH	Particle size—small
HO - C - H	Distribution—Extracellular H_2O
HO - C - H	Glomerular Filtration—Free
C - OH	Tubular Reabsorption—None
C - OH	Metabolism—Essentially None
CH_2OH	Pharmacologic Activity—Inert
	Toxicity—None reported

..*Fig. 2*: See text.

small particle which therefore obligates a large volume of water per unit absolute weight. Since the mannitol cannot be reabsorbed across the tubular epithelium, it must traverse the length of the nephron within the tubule carrying with it the fluid it obligates. The excretion of mannitol and its obligated fluid constitutes an osmotic diuresis. In contrast to solutes such as urea and sodium chloride, the limited distribution and lack of tubular reabsorption of mannitol make it ideal for the production of osmotic diuresis.

Therapy For Oliguric Patients (Treatment of Functional Renal Failure)

Frequently, the physician is confronted with a patient already oliguric (urine flow less than 20 ml per hour). Common precipitating factors include automobile accidents, burns, and other trauma. In the past, a diagnosis of irreversible renal failure was made in such oliguric patients when the scant urine was hypotonic and contained low concentration of urea and inappropriately high concentration of sodium. The restrictive renal failure regimen was usually applied to these patients.

In a study of 101 patients tentatively given a diagnosis of acute renal failure, we attempted to produce diuresis using the osmotic diuretic mannitol. A test dose of mannitol consisting of 12.5 Gm of a 25 per cent aqueous solution or 20 Gm of a 20 per cent aqueous solution was administered intravenously during a three-to eight-minute interval. If urine flow increased to 40 ml per hour or more in response to the test dose, mannitol was administered either continuously or by 20 Gm increments as needed to maintain urine flow at approximately 100 ml per hour. Mannitol therapy was discontinued when the patient was able to maintain this rate of urine flow without the aid of mannitol. In patients responding with an increase of urine flow less than 40 ml per hour, re-evaluation was performed and a second test dose administered. In patients not responding to the initial or second test dose, the classic renal failure regimen was applied.

A sustained diuresis was produced by mannitol infusion in approximately two-thirds of the patients (Table 1). Two

TABLE I: RESPONSE TO MANNITOL FOR DIURESIS IN 101 OLIGURIC PATIENTS

Methods	Success	Failure	Totals
Test Dose*	9	17	26
Titration**	61	14	75
Totals	70	31	101

*12.5 Gm in 3" or 20 Gm in 8".

**Constant or intermittent infusion 20 por cent mannitol.

Only patients in whom diuresis was sustained and management not restricted by oliguria are included in the "success' column.

examples are presented in Figures 3 and 4. In the remainder, diuresis was not secured. In several patients for whom a sustained diuresis was produced, azotemia, depression of urea clearance and salt wasting persisted for as long as fourteen days. These findings suggest that these patients experienced acute organic renal damage but that mannitol maintained a high urinary output and circumvented the need for the classic renal shutdown regimen (3). Based on our experience to date, the following tentative recommendations may be made: Urine flow

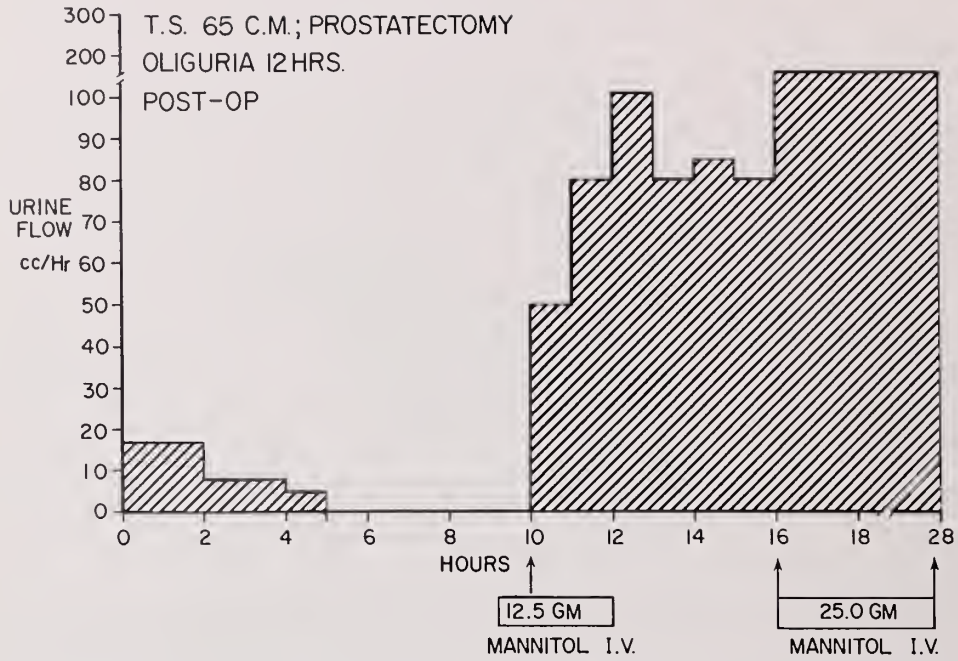


Fig. 3: This sixty-five-year-old male had developed rapid atrial fibrillation and pulmonary congestion associated with postoperative fluid administration. Mannitol diuresis was effective in clearing the signs of acute congestive failure as well as increasing urea clearance and urine flow.

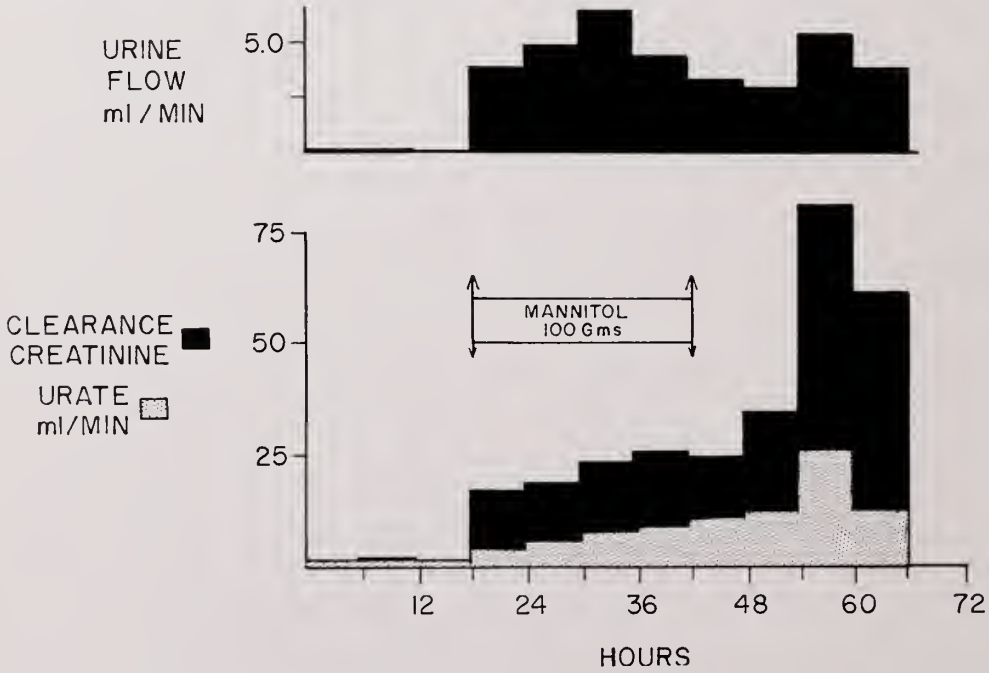


Fig. 4: An eighteen-year-old male following Methotrexate therapy for granulocytic leukemia developed acute uric acid nephropathy. Serum uric acid and urea nitrogen rose to 47 and 101 mg per 100 ml, respectively. During the eighteen hours before mannitol therapy, the patient remained essentially anuric despite intravenous infusion of four liters of alkaline fluid. Mannitol diuresis was associated with a prompt decline in serum uric acid and urea nitrogen.

should be considered a vital sign in all critically ill patients and all patients in a high risk category. Oliguria, when detected, should be promptly treated by the use of mannitol diuresis coincident with other resuscitative procedures. The physician should not wait to observe whether or not the effect of hydration or restoration of blood pressure alone will restore urine flow, since this delay may permit a reversible oliguria to become irreversible. Urine flow should be maintained at approximately 100 ml per hour with electrolyte replacement as needed in all these patients. No oliguric patient should be denied a test dose of mannitol since there is no clinical method to forecast the response and this dose is innocuous. On the other hand, no more than 100 Gm of mannitol should be administered per twenty-four hours unless a diuresis of greater than 100 ml per hour is obtained. In patients receiving 150 to 300 Gm of mannitol in less than twelve hours but unable to excrete more than 50 to 60 ml per hour in response to these doses, a clinical picture resembling water intoxication has occurred (4).

Management of Surgical Patients

Some clinical conditions associated with acute renal failure such as burns, accidents of pregnancy and most forms of trauma are not anticipated events and renoprotective measures can not be instituted a priori. However, anesthesia and surgery are planned events known to cause acute depression of renal function for which prophylactic renoprotective measures can be applied.

The high incidence of lethal renal failure following abdominal aortic aneurysmectomy gave impetus to investigation of renal function during and following the procedure. It was found in dogs that hydration prior to application of renal insult offered some renoprotective effect and infusion of 1000 to 1500 ml five per cent dextrose in water given prior to anesthesia for abdominal aortic aneurysmectomy was empirically used by many vascular surgeons. A comparison of this measure with mannitol diuresis was made in a control study (Figs. 5 and 6). Whereas mannitol infusion maintained diuresis, glomerular filtration rate, and effective renal plasma flow, the effect of water loading was transient and severe oliguria occured during and following aneurysmectomy (5). During the past three years, mannitol diuresis as a renoprotective measure for these patients has become routine in our hospital. Despite an increased number of procedures, not one case of acute renal failure following aneurysmectomy has occurred.

The aneurysmectomy experience encouraged study of surgical patients with chronic renal impairment. Acute depression of renal function may accelerate parenchymal damage in such patients. The prophylactic effect of sustained hydration and mannitol diuresis during surgery was studied in six patients with chronic depression of glomerular filtration rates. Less than 100 Gm of mannitol was required to maintain glomerular filtration rates at contral levels (Table 2). Postoperative study failed to reveal any deleterious renal effect of the surgery (6).

Earlier attemps to prevent oliguria using water and physiologic infusions during anesthesia and surgery were disappointing. Production of cardiocirculatory overload

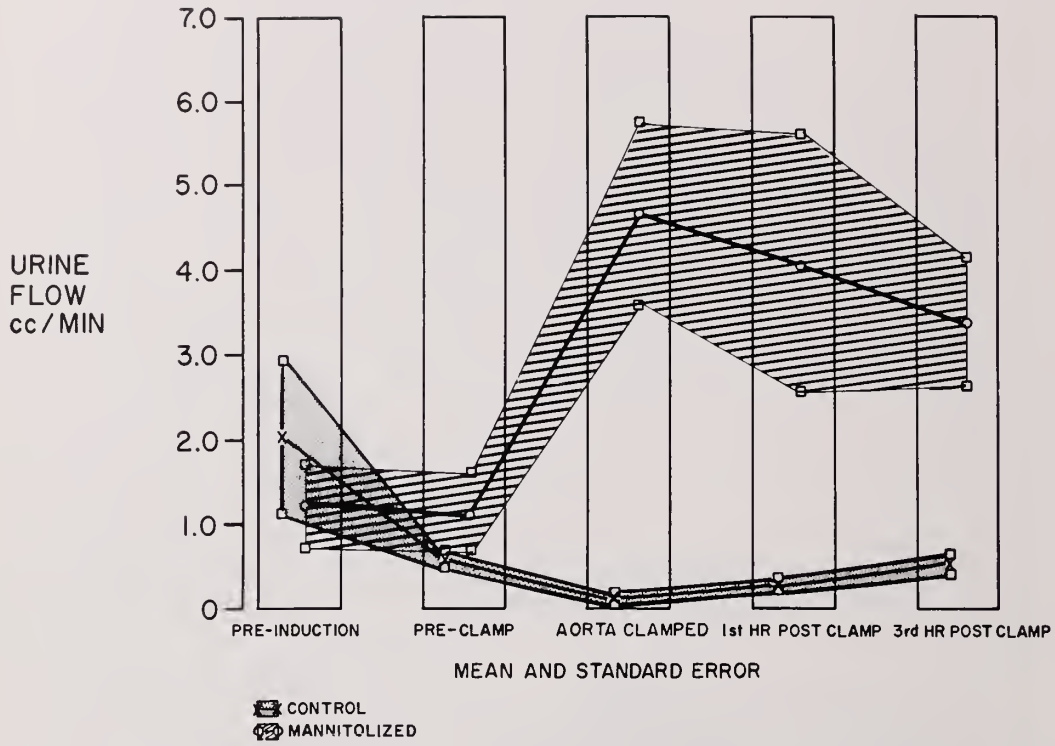


Fig. 5: A comparison between a control and mannitol treated group (five patients in each group). Diuresis produced and sustained by mannitol infusion maintains intratubular pressure, volume, and dilution of solute, factors which may counteract mechanisms responsible for acute renal failure.

and water intoxication in some patients so treated led to acceptance of oliguria as an inevitable occurrence (7, 9). The restriction of fluids and sodium chloride from several hours prior to induction of anesthesia to a few days postoperative became an inviolate requirement in most hospitals.

The knowledge that mannitol diuresis can be produced even in poor risk cardiac and renal patients has permitted us to renew investigation of the effects of fluid administration during anesthesia and surgery; the subject's welfare can be safeguarded if circulatory overload appears imminent by stopping protocol fluid administration and starting mannitol diuresis.

A controlled study of renal function during halothane anesthesia and surgery was designed to compare the effects of sustained hydration (Group II, six subjects) with those of traditional fluid restriction (Group I, six subjects). The results (Table 3) demonstrate that at all concentrations of halothane studied renal plasma flow, glomerular filtration rate and urine flow were significantly depressed in fluid-restricted subjects. In contrast, depression of these measurements in hydrated

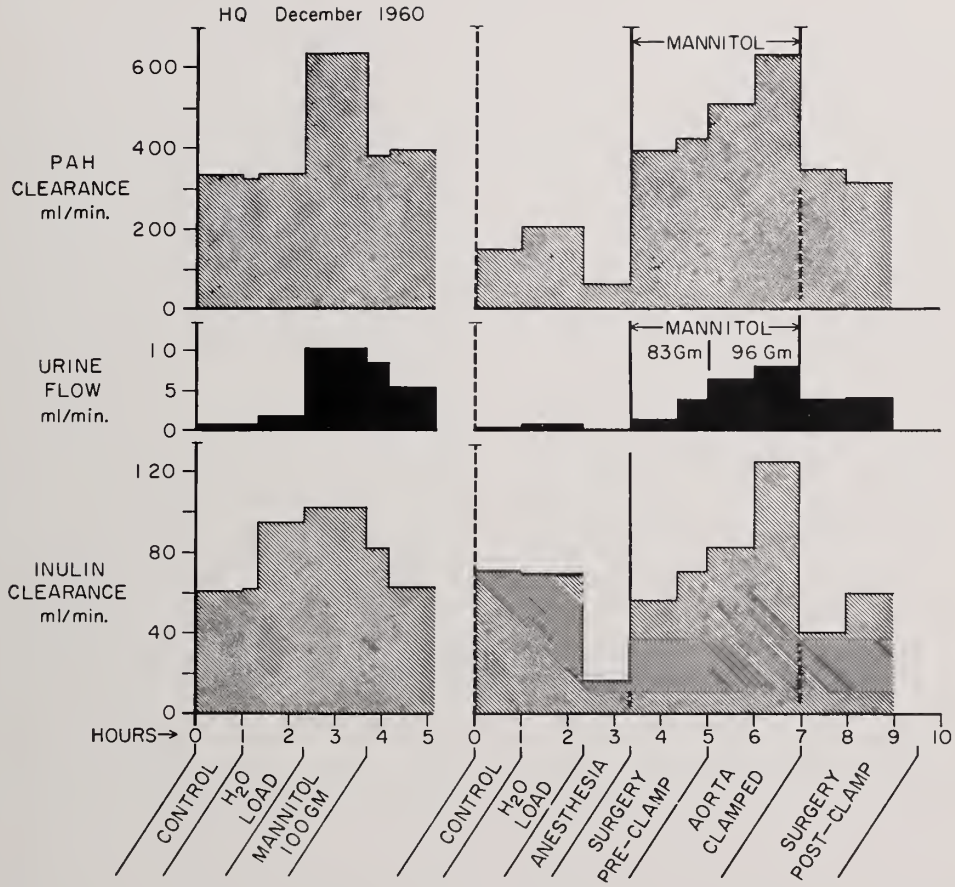


Fig. 6: An example of a mannitol treated patient. Mannitol diuresis during surgery is associated with return of renal plasma flow (C Pah) and glomerular filtration (C Inulin) toward normal.

TABLE II

Patient	Glomerular Filtration (Cer) Surgery	Glomerular Filtration (Cer) During Surgery	Mannitol Administred (Gm.)	0.3% NaCl Infused (ml.)	Urine Volume (ml.)
1	71	71	40	4,200	2,610
2	68	72	85	4,270	2,560
3	64	101	60	2,740	1,360
4	51	37	30	3,690	2,460
5	42	54	65	3,540	2,210
6	51	56	76	3,750	1,770
Mean	58	65	60	3,700	2,150

In these six patients with chronic renal impairment, urine flow and glomerular filtration were maintined during the twenty-four hours encompassing surgery. Prior to anesthetic induction, hydration was established by the intravenous infusion of 0.3 per cent saline in an amount to equal overnight urine volume plus 10 ml/Kg body weight. Thereafter, hydration was sustained by matching infusate with urinary volume and insensible loss. Relatively small amounts of mannitol were required to maintain urine flow at approximately 100 ml/hr.

subjects occurred only in response to high concentrations of halothane and was promptly reversed by decreasing the anesthetic concentration.

Relatively young patients without cardiovascular diseases were selected for the hydration study. Interpretation and clinical application of our results must be conditioned by this selectivity. In this group sustained hydration not only maintained diuresis, but also renal perfusion and glomerular filtration except when the anesthetic concentration used was increased beyond usual clinical levels. Even at high anesthetic concentrations, diuresis persisted and the depression of renal perfusion and filtration was promptly reversible. Hydration and diuresis were sustained for a few days following surgery until the danger of renal depression was passed (9). When the physician has a choice (without risk to the patient) between maintaining or permitting depression of renal perfusion during surgery, it is reasonable to choose maintenance. This may be accomplished, at least in the category of patient and procedure reported, by sustained hydration. Current studies not yet completed suggest that for older patients with cardiac and renal disease hydration alone will not always maintain renal hemodynamics and supplemental mannitol diuresis is required.

An understandable reluctance to hydrate the surgical patients exists since it is well established that water and saline loading during and after surgery usually does not produce diuresis but may cause fatal pulmonary edema or water intoxication. There is no real discrepancy between our results and studies demonstrating the inability of the surgical patient to excrete water loads. The apparent discrepancy is resolved when

TABLE III: EFFECT OF HYDRATION ON RENAL FUNCTION AT TWO LEVELS OF HALOTHANE CONCENTRATION

Group I: Dehydrated n = 6

Group II: Hydrated n = 6

	Control		Halothane 0.5 - 1.0%		Halothane 1.2 - 3.0%	
ml/min.	Gp I	Gp II	Gp I	Gp II	Gp I	Gp II
C-PAH	550	471	213	415	168	251
	p	0.10	p	0.05	p	0.10
C-I	114	91	59	84	48	55
	p	0.10	p	0.05	p	0.10
Urine Flow	16.1	14.4	0.6	3.3	0.5	2.9
	p	0.10	p	0.05	p	0.05

Results obtained in dehydrated and hydrated patients compared for the control day and day of surgery. To minimize the effects of anesthesia per se, the halothane concentration used in each patient was varied periodically throughout the operative procedure.

the timing between starting hydration and anesthetic induction is considered. In our Group II subjects, support of the central circulatory volume and diuresis by hydration was established *before* and continued during anesthesia and surgery. Water and solute administration were started *after* anesthetic induction or not sustained in studies not productive of diuresis. It is suggested that if hydration is delayed until *after* anesthetic induction, critical reduction of the central circulatory volume has already occurred. The resultant sympathetic vasoconstriction and decrease in renal perfusion is independent of the central circulatory volume and its expansion will produce cardiocirculatory overload rather than diuresis. A somewhat similar timing relationship exists in animal experiments in which mannitol infusion is renoprotective only if given before or simultaneously with the renal insult.

Confirmation of our results and the proposed mechanisms must be accomplished. At this time, tentative clinical recommendations include: Sustained hydration (15 ml/Kg body weight) for surgical patients *prior* to anesthetic induction supplemented by the intermittent infusion of 12.5 Gm of mannitol as required to maintain urine flow at 100-120 ml per hour during and for a few days following surgery. Overhydration of the patient must be avoided as assiduously as underhydration. When hydration does not produce diuresis or when urine flow decreases despite sustained hydration, mannitol rather than large volumes of fluid should be used to institute or reestablish urine flow. This procedure, combined with solute replacement and conventional surgical management has been safe and effective in maintaining renal perfusion and urine flow until danger of renal failure is passed.

The present and previous reports do not elucidate many complex mechanisms operative in control of homeostasis and renal function. They do suggest a practical and safe prophylactic approach to renal failure. Sustained diuresis during and for a few days following potential renal insult not only protects renal function, but simplifies management.

Summary

Our cumulative studies suggest that urine flow should be considered a vital sign in patients who have been exposed to factors known to precipitate acute renal failure. Urine flow of approximately 100 ml per hour should be maintained in such patients by judicious use of the osmotic diuretic mannitol and hydration.

Traditional fluid restriction in the surgical patient should be abandoned: Anesthesia and surgery acutely depress renal function and are occasionally followed by lethal renal failure. Sustained diuresis, established prior to anesthetic induction by hydration and supplemented when needed by mannitol infusion, protects the surgical patient against acute renal failure.

There is an urgent requirement for application of effective prophylactic methods for acute renal failure since the mortality rate of this dread condition remains above fifty per cent.

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ADVANCES IN PROSTHETIC TECHNOLOGY

Cameron B. Hall, M.D.

The number of individuals requiring artificial arms and legs has steadily increased on a world-wide basis during the last three decades. The incidence of trauma, both civilian and military, disease, and birth defects producing limb deficiencies has risen in both children and adults, while acceptance of such loss without prosthetic replacement has diminished. Advances in individual and government responsibility for the afflicted, expansion in medical and paramedical knowledge of the problem, and utilization of the constantly expanding techniques and materials to be found in the scientific and manufacturing fields has led to continued progress in prosthetic technology.

The Problem

The patient shown in Figure 1, a bilateral congenital shoulder disarticulation with a right lower extremity phocomelia, obviously requires the maximum in prosthetic replacement of the upper extremities. Aside from cosmetic considerations, what specifically are we seeking? The mechanical replacement of limb segments so articulated as to replace the missing bone and joint elements is not difficult to achieve. A wide assortment of materials constructed to well-accepted designs using established techniques will, in most of the civilized nations, produce a prosthesis similar to those seen in Figure 2a and b. Structurally, we have replaced the missing extremities, but what is grossly inadequate here (1, 2, 3, 6)?

Power: Generated by the patient's residual structures, sufficient force and excursion is available for the activation of one side only, and the resultant power is less than 10% of that seen in the extremity of a normal boy his age. The second prosthesis is passive.

Control: Body movements and accessory control-lock motions are gross and energy-consuming. Fine movements with even basic coordination are quite beyond the abilities of the majority of such patients.

Feedback: Knowledge of the position in space and of the current activity of any and all parts of the prosthesis is perceived by visual clues only. Some proprioception is derived by socket-wall and harness pres-

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Fig. 1: This congenital bilateral shoulder disarticulation with a phocomelia of the right lower extremity requires the utmost in prosthetic replacement. Power and control from available somatic sources are minimal.

sures, but compared to the high sensory output of the normal extremity, this is indeed minimal.

The replacement or substitution for muscular power, neurological control, and sensory feedback provide the major unsolved problems in the artificial limb field today. What are some anticipated solutions?

Power

Developments in this area, while still experimental to a degree, have been quite successful and offer some hope for the future. In order to provide adequate sources of energy, the following should be considered:

1. *Patient-generated power*: Numerous refinements in the harnessing of motion of one body part in relation to another have been developed. Friction-free pulleys and guides, durable cable systems, and "comfortable" harnesses increase the efficiency of this readily available power source. The overall efficiency is still deplorable in terms of true output as compared to amputee fatigue.

2. *Pneumatic power*: Compressed gas, usually carbon dioxide stored in relatively light, small containers, have produced sufficient energy to drive small motors, pistons, and artificial muscles of the McKibben type.

3. *Electric power*: Battery-stored electrical energy has been utilized to run small, powerful motors of sufficient power to activate the joints and prehension devices of upper extremity prostheses.

4. *Electro-pneumo-hydraulic power*: This combination provides a fluid tension actuator deriving benefits from the best features of these energy sources. Micro-motors, pistons, vanes, and artificial muscles are available. The storage and replenishment of these energy types is something of a problem, but is not insurmountable, and these devices are in daily use.

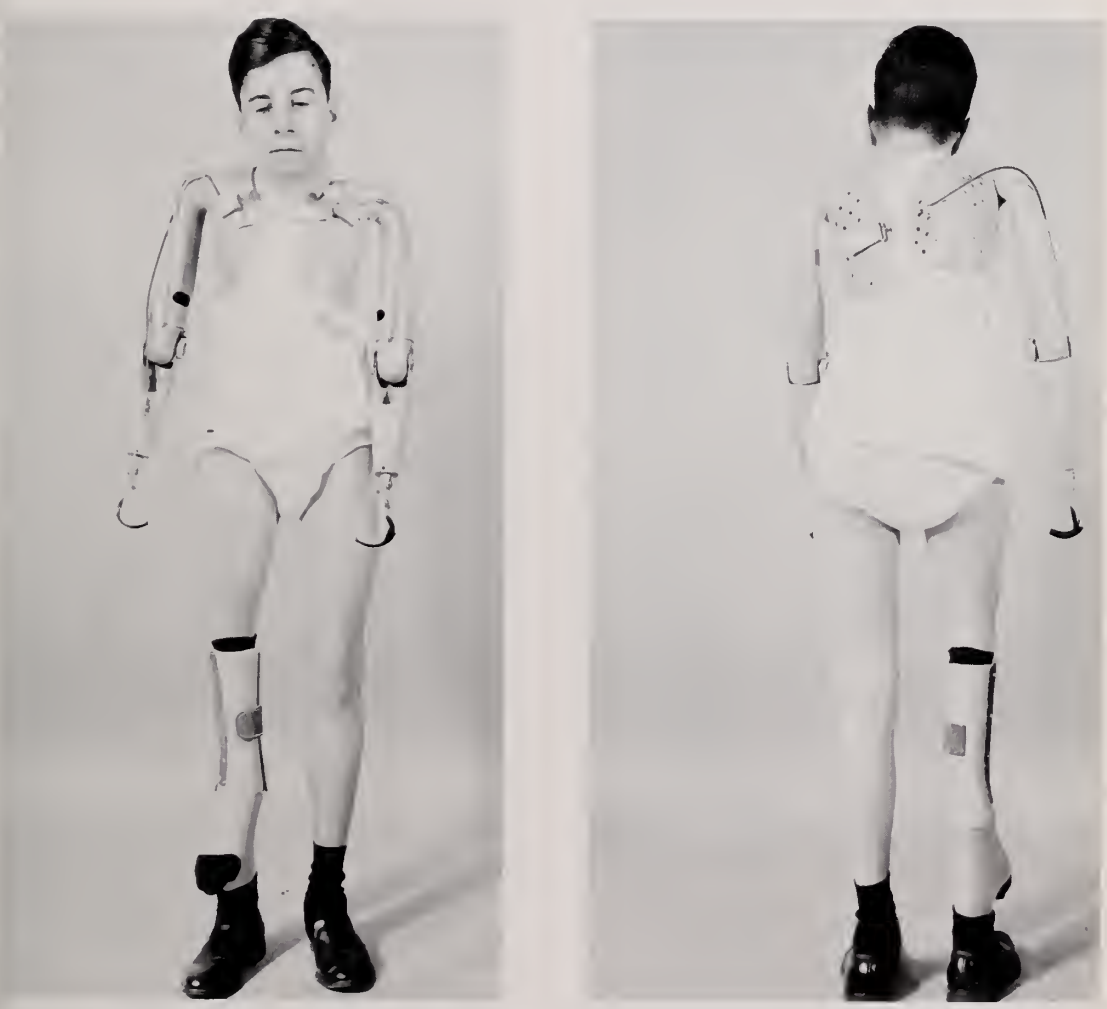


Fig. 2a,b: Present tecniques provide power and control to one prosthesis only; the other is passively control with sensory feedback is the ultimate goal operated. Efficient external power under accurate in the fitting of similar patients.

Control

Control, to date, seems a much more difficult dilemma. The amputee should have volitional, proportional and vectorial control over his prosthesis (10).

Volitional control includes the instantaneous ability to start, stop, and modify the motion of the prosthesis by the amputee.

Proportional control permits the amputee to vary his own control motion and

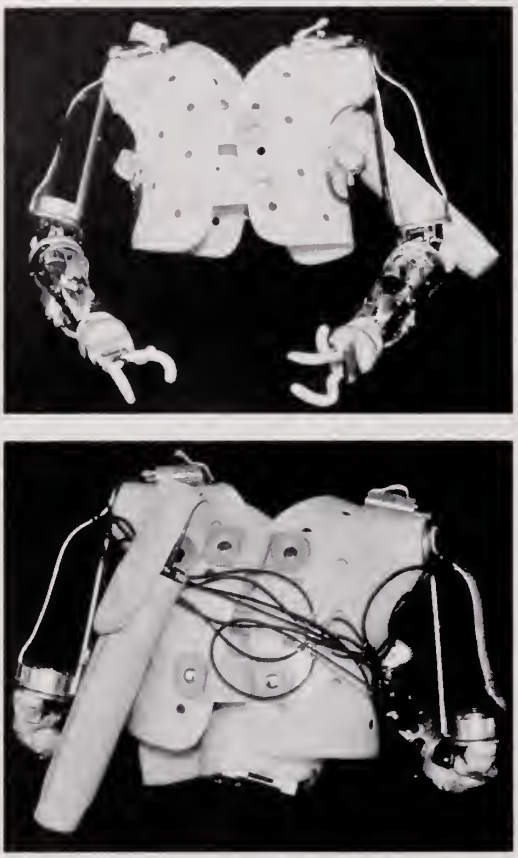


Fig. 3a,b: The so-called Heidelburg Arm., developed under Dr. Ernst Marquardt, is, to date, the most successful application of external power (carbon dioxide gas) to the upper-extremity prost heses of children. Humeral rotation, elbow flexion, forearm pronation and supination, and terminal device prehension are under the complete control of well-trained four-year-old patients.

thereby vary the rate, extent, and force of the prosthetic movement.

Vectorial control allows a particularly complex movement to be achieved in a smooth, direct fashion, rather than by a sequence of motions about various axes.

Types of control available to an amputee would include the following:

1. *Somatic movements*: Motion of one part of the body relative to another part, motion of one body part relative to a fixed base, and motion of one body part relative to space, are the three essential forms of somatic movement practical for use (6). The musculoskeletal remnant of a missing part can be utilized in a logical sequence to control the external source of power. An excellent example of this type is seen in Dr. Ernst Marquardt's carbon dioxide gas-powered prosthesis for bilateral phocomelias of the shoulder disarticulation level (Figure 3a,b) (7). Shrugging the should ers forward produces internal rotation of the humeral elements, bringing the hands together in front of the body. Shrugging the shoulders back produces external rotation of the humeral shafts. A motion forward, as if to grasp, activates the terminal device; retraction opens the device. Motion of the head to the contralateral side, activating the nudge control, flexes the ipsilateral elbow.

Analysis reveals that activation of a unilateral shoulder disarticulation prosthesis requires twelve different movements of the shoulder girdle or vertical column. Voluntary movements include:

a) Closing and opening the prehension device.
b) Pronation and supination of the forearm.
c) Flexion and extension at the elbow joint.
d) Locking and release of the shoulder joint.

Passively-adjusted movements include:

a) Braking or friction control of the passively-operated humeral internal or external rotation.
b) Braking or friction control of passive shoulder abduction.

A simple analysis reveals that a *bilateral* shoulder disarticulation amputee, controlling his prostheses by somatic movement alone, requires *twenty-four* different motions.

2. *Muscular contraction*: Contractions of muscles increase their bulk, and this expansion can be sensed by small devices called *transducers* which harness this small motion and force to activate power sources. The types of transducers available for this small motion utilization are as follows:

a) CO_2 valves
b) Miniature electrical switches
c) Strain gauge semiconductors
d) Mercury switches
e) Photoelectric cells
f) Carbon compression
g) Potentiometers
h) Inductance sensors
i) Differential transformers
j) Capacitance sensors
k) Touch plates

The Heidelburg arm of Marquardt uses the CO_2 valve. The electrical hand developed by Wilms at Vaduz Lichtenstein and more recently improved in Paris, and some of the electrical arms developed in the United States, use the miniature electric switches (8).

3. *Myoelectric signals*: Four areas in the body, among other electrogenic tissues, are ordinarily measured for their electric potential: the brain, heart, nerves, and striated muscle. Striated muscle is possibly the most promising in furnishing signals as a source of control of external power. Electrical manifestations of their voluntary activity are easily recorded and they can be varied to a remarkable extent. The Russian electrical arm is an example of the harnessing of signals from the flexor and extensor muscles within the amputation stump to open and close a prehension device.

4. *Voice control* is an exciting field, particularly because of its possible employment by astronauts where extreme G-loadings may prevent the use of extremity motion. Pitch, volume, and duration offer the variation necessary for alteration of commands. Its possible use in the paraplegic is obvious.

One or several of the above features has been utilized on a limited basis in the products of prosthetic laboratories in Russia, Roehampton, Cleveland, and Toronto.

Feedback

This is an area where little progress has been made. Some idea of the difficulties involved may be realized by the amazing fund of information a man derives from putting his hand in his pocket. Without the use of visual clues, the only sensory device available to the amputee, he can tell one in which pocket the hand lies, the nature of the pocket fabric, its state of repair, depth, width, and state of cleanliness; the contents including weight, size, texture, number, degree of moisture, durometer, finish, and worth (if it includes coins) of each individual object; and can



Fig. 4: These plastic forearm components, developed at the Child Amputee Prosthetics Project, University of California, Los Angeles, are inexpensive, can be readily manufactured, and allow easy fitting with simple tools. They are clean, light, and durable.

selectively grasp or reject one or a given number of the objects to be withdrawn from the pocket. It would seem that many years of intensive work lie ahead before a prosthesis can impart this information to its wearer.

Recent Products

Of interest among the recent developments at the Child Amputee Prosthetics Project, University of California at Los Angeles (9), are the following items shown in Figure 4. All are formed from plastics of various types. The transparent forearm socket is formed from a tube of Lexan, a polycarbonate plastic that can be softened with heat, molded over a plaster mold of the amputee's stump, and applied in a matter of minutes. It is shatter-resistant, inexpensive, and requires minimal skill or training to obtain an extremely accurate fit. The plastic foam cover reproduces the normal body contour, the outer layer of plastic resembles skin, and the plastic prehension device can be passively or actively harnessed.

In Figure 5, a powered cart for the severely-handicaped amputee reveals com-



Fig. 5: Controlled by the great toe, the maneuverability, adjustable height, and small size of this battery-operated cart permits its use with normal household furniture. It is easily transported in an automobile.





Fig. 6a,b: The severely-handicapped child grows into the severely-handicapped adult. Developed at the Child Amputee Prosthetics Project, UCLA, these controls have been installed in an automobile of conventional design. The patient is a fully-licensed driver.

plete control in all directions of travel plus an ability to raise and lower the seat through a simple panel activated by the patient's big toe. Power is derived from a battery, easily charged at night.

The automobile shown in Figure 6 is a standard model modified for use by a severely-handicapped bilateral shoulder disarticulation patient with gross bilateral leg lenght deficiencies. All controls are foot-operated. The patient is completely self-sufficient and is licensed by the Motor Vehicle Department of the State of California.

A report on recent advances in the prosthetic field would be deficient without mentioning the immediate post-surgical fitting techniques of lower extremity amputees developed by Berlemont in France, modified by Weiss in Poland, and under extensive development by Burges in the United States (4). The technique requires meticulous attention to detail, but offers significant benefits in reduction of post-operative pain, rapid resumption of ambulatory activities and the production of strong, non-tender stumps. The advantages to both the patient and the medical profession are obvious.

Summary

A few of the significant advances in the armamentarium and techniques for the successful rehabilitation of limb-deficient pa-

tients have been discussed. The areas in which additional progress will be made, particularly in the fields of upper extremity prosthetic power, control, and sensory feedback, have been indicated.

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A NEW INSTRUMENT FOR AUTOMATIC MONITORING AND TAPE RECORDING IN INFANTS AND CHILDREN

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Louis Lemberg, M.D.
Herbert Burack, M.D. and
Barouh V. Berkovits, E. E.

The recent explosive development of controlled electricity in medicine has opened many avenues in the monitoring and treatment of patients. A growing number of instruments are currently employed for continuous monitoring of vital clinical and physiological events in the acute cardiac and postoperative patient (1-3).

In contrast to widespread use in adults, monitoring has not been widely used in infants and children. Continuous monitoring may, however, reveal underlying cardiac or metabolic abnormalities. In 1963 Robinson and Barrie (4) emphasized that during exchange transfusion more efficient methods of monitoring the electrical activity of infants would be of interest. Electrocardiographic changes may occur during exchange transfusion. Continuous electrical monitoring could provide an early and accurate warning of impending danger, thus minimizing the hazards of this procedure. Stephenson reviewed 1770 cases of cardiac arrest (5). Close to one fourth occurred in children under 10 years of age.

The cardiac surgeon and anesthesiologist have long recognized the usefulness of continuous monitoring during surgical procedures. Rakow, Slanitri and Green found cardiac arrest during surgery to be more frequent under one year of age (6). Greenberg reported 20 cases of cardiac standstill during operations or anesthesia in infants and children (7).

Description of the Instrument* (Figure 1)

The component parts that make up the instrument are:

1) Oscilloscope, 2) Rate meter, 3) Electrocardiograph, 4) Tape Recorder, 5) Cardiac Pacemaker An electrocardiographic lead selector permits the display of any electrocardiographic lead on a 10 inch oscilloscope at a speed of 25, 50 or 100 mm per second. A permanent electrocardiogram of the lead shown on the oscilloscope can be obtained when desired. A standard electrocardiographic amplifier is employed.

This study was supported by a Grant from the Heart Association of Greater Miami

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American Optical Company, Chelsea, Massachusetts, U.S.A.

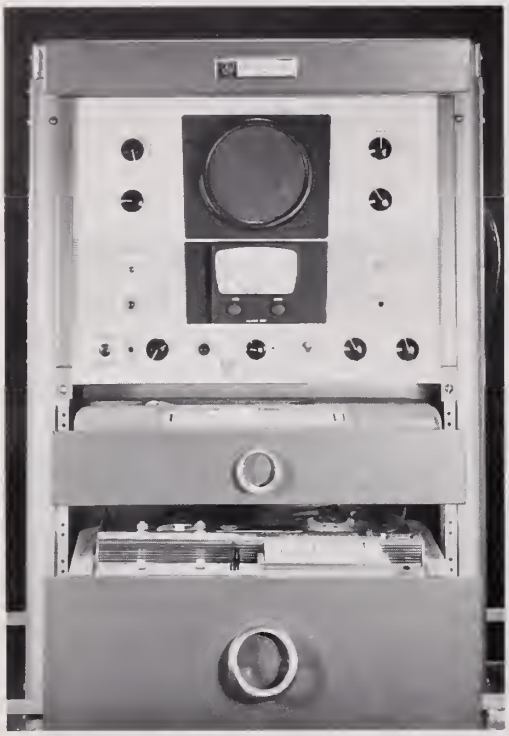


Fig. 1: Photograph of the instrument.

Proper adjustment of the sensitivity dial allows for heart rate readings directly from the rate meter. A beeper, synchronized with every ventricular contraction, provides acoustical signals which are additional to the visual aids in detecting sudden changes in rhythm. An audible warning is provided when upper or lower heart rate limits are passed. Although not available in the present model, an extrasystole counter has been included in the latest units. A contrasting sound pitch distinguishes the tachycardia from bradycardia. The electrocardiogram is constantly recorded on tape with each one providing eight hours of continuous monitoring. The tape can be played back at any convenient time, all signals being displayed on the oscilloscope screen and rate meter. The electrocardiogram obtained during playback does not lose any of its original characteristics, thus confirming the fidelity of the recording system (Figure 2).

A portable cardiac pacemaker* included with the instrument for internal (transvenous) use, stimulates only when needed (8). Electrical stimuli thus, pace the heart only after a pre-set interval following a preceding ventricular depolarization has been exceeded. Pacing automatically discontinues when the natural rate exceeds the artificial pacemaker rate, for one or for several beats, Stimulation is resumed automatically and instantly when the natural rate drops below the rate of the artificial pacemaker. Needless continuous stimulation as well as competition between natural and artificial beats is thus obviated. This modified pacemaker has parameters similar to those of ordinary commercial instruments and has been fully described elsewhere (8). It can be used also for continuous pacemaking.

A 24 hour Esterline Angus type of recording instrument indicates on slow moving paper the time of pacemaker activity, which is also indicated in the tape. Therefore the periods of intermittent pacemaker activity can be rapidly checked out in the tape recording without requiring playing, back the whole reel.

Comments

The new instrument described above has several advantages over those currently available. First, it obviates the need for counting the heart rate with a stethoscope, a method still in use in many pediatric centers (4). Second, it permits the thorough study of the electrocardiogram without the limitations imposed when only a single lead is available for analysis. Experts in the field of electrocardiography have long recognized that the hallmarks of certain arrhythmias or electrolyte disturbances can be present in some leads while absent in others. The lead selector of the instrument obviates this difficulty for it permits instantaneous switching from one lead to another.

With little training the electrocardio-

**American Optical Company — Demand Pacemaker*

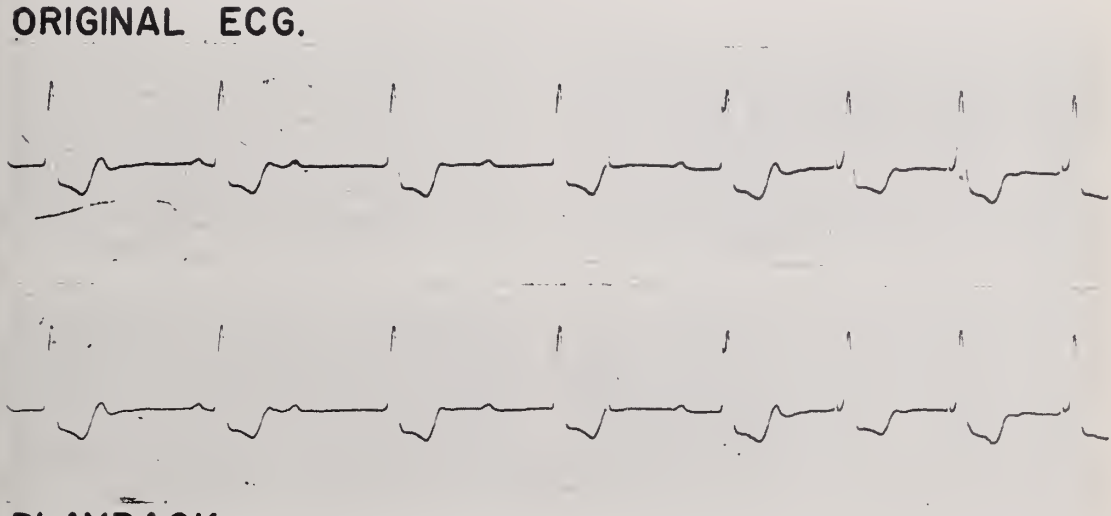


Fig. 2: Initiation of continuous pacing in patients with post-surgical complete heart block. Note the stricking resemblance between the original electrocardiogram on top, and the one recorded during tape playback (bottom).

graphic deflections can be identified on the oscilloscope screen without requiring a continuous trace on electrocardiogram paper. However, tracings can be periodically obtained for subsequent restudy. Of major importance in this new instrument is the feature which enables the study and analysis of important events on tape playback, which may not have been initially apparent. Careful analysis may then shed light on the mechanism under consideration, as well as the events which preceded (and could have led to) any untoward effects. Examples of this can be non-specific changes leading –to definite electrolyte imbalance in some infants, as well as the natural history of ventricular fibrillation or cardiac arrest in surgical or post-surgical patients. The fidelity of the tape recorder can be seen in Figure 2 where the original electrocardiogram is compared with the tracing obtained during playback.

A final advantage is the inclusion of a different type of cardiac pacemaker which works only when required (on demand). This artificial escape pacemaker, which imitates natural occurring phenomenon, delivers impulses automatically whenever the natural beat fails, irrespective as to whether the failure occurs during a single beat or for long periods of time lasting hours or even days. However, it will stop by itself if the natural rate exceed the preset pacemaker rate. This feature will avoid the unnecessary interference betwen two different rhythms, which occurs when high degrees of A-V block disappear (a not usual phenomenon). This is helpful because the average ventricular rate is not kept at high, dangerous levels, and mainly because it

prevents pacemaker stimuli from falling in the vulnerable phase of the ventricles and hence inducing severe ventricular arrhythmias. This eventuality was considered rare in the past because it was thought that the intensity of commercial pacemakers was usually below repetitive firing threshold. However, it should be remembered that repetitive firing can occur either because the intensity is decreased or because the threshold is reduced. It is now well known that the latter is markedly reduced by drugs (Isoproterenol, digitalis, toxic doses of quinidine) anoxia and ischemia (8).

The Demand Pacemaker is particularly useful in the intermittent A-V blocks seen in children mainly in post-surgical and post traumatic block.

The new instrument for automatic monitoring and pacemaking on demand has been used in 31 infants and children. The clinical results will be presented subsequently. The recordings obtained have been found most satisfactory in older children and during short term monitoring. In three small, restless, infants, with tendency to low electrocardiographic signals, false alarms occurred frequently. They were thus not included in the present study. The frequency of the latter can be reduced by transiently immobilizing the left leg and recording with the switch in the aVF position.

Summary

A new type of electrophysiological monitor for infants and children is presented. The electrocardiographic deflections are displayed on a large oscilloscope screen and recorded simultaneously on tape. A built-in portable pacemaker which turns itself on and off when required is also included. An Esterline Angus type of recorder provides for rapid scanning of tapes during playback. This instrument is particularly helpful in the following situations:

1) During exchange transfusion. 2) During anesthesia and cardiac surgery. 3) During the persistence of post-surgical arrhythmias. 4) In instances of iatrogenic or traumatic A-V block. 5) During the study of individual homeostatic capacity in cardiac response in neonates (9).

Resumen

Se presenta un nuevo tipo de monitor electrocardiográfico para ser usado en recien nacidos y niños mayores. El electrocardiograma se puede observar directamente en la pantalla del osciloscopio a la vez que se graba en cinta magnética. Un trazado en papel a velocidad de 25 milímetros por segundo se obtiene ya sea directamente del paciente o posteriormente cuando se estudia la cinta magnética. Otra característica de este instrumento es la de tener incorporado dentro de si mismo un marcapaso artificial que trabaja solamente por demanda. El funcionamiento del mismo se estudia por una señal que éste hace en la cinta, facilitando así el tiempo de lectura de la misma.

Este nuevo monitor es de especial importancia en los siguientes casos:

1) Durante la transfusión exanguínea
2) Durante la anestesia y cirugía
3) En el post-operatorio de las operaciones cardiacas a cielo abierto

4) En los casos de bloqueos avanzados traumáticos o miocardíticos que requieran marcapasos internos.
5) En el estudio de las alteraciones homeostáticas de los recien nacidos.

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CASE REPORT

GUNSHOT WOUND OF THE HEART SUCCESSFULLY TREATED

José L. Iturrino, M. D.,
Urselio Alvarez, M. D.,
David Latoni, M. D.,
Félix Rivera, M. D., and
E. Feliciano, M. D.

Not infrequently the surgical literature has been enriched by reports of successfully treated penetrating wounds of the chest involving various intrathoracic structures. Boyd and Strieder (1) as well as Lui et al (2) have given us recent examples of the above stated situations. Because of the relative rarity of survival following bullet wounds of the heart, especially when the atria are involved, we have decided to report a case of ours in whom a tear in the right atrium, produced by a .38 caliber bullet, was repaired and the patient recovered satisfactorily.

Case Report

The patient was a 56-year old white man, a Cuban refugee, brought to the emergency room of Bella Vista Hospital, at 11:20 A.M. on April 20, 1965, approximately 20 minutes after being shot in the precordial region at the level of the xiphoid cartilage where there was market tattooing present indicative of close-range firing. The weapon had been a .38 caliber Smith & Wesson revolver.

Physical examination disclosed that the patient was extremely pale, with circumoral cyanosis, and conscious, but with a foggy sensorium. The blood pressure was 80/40 mm Hg and the pulse 136/ min. Copious amounts of bloody sputum obstructed the airway. There was an exit wound at the posterior aspect of the right shoulder from where a moderate amount of bleeding was observed. Auscultation revealed again the presence of marked tachycardia. No murmur was detected. The breath sounds were present but they were distant bilaterally. The cervical veins were not distended. The pulse was not of the paradoxical type.

While in the emergency room a venous cutdown and a tracheostomy were performed. Blood was drawn for hemoglobin, hematocrit, type and crossmatching, and a Dextran infusion was started. The cutdown was done while the patient was lying on the X-Ray table and a chest X-Ray was taken that revealed haziness of the right hemithorax with a clear left hemithorax. The patient was then taken to the operating room, rapidly anesthetized and positioned for a right posterolateral thoracotomy through the fifth interspace. The right pleural cavity was found to contain blood and blood clots that totaled approximately 3,000 cc's. There was a pulmonary hematoma involving the right middle lobe from where brisk bleeding was noticed. A comminuted fracture of the fourth rib posteriorly was present at the level of the exit wound. The pericardium was seen to contain blood as well as having a through and through perforation of about 1.5 cm. in diameter. After opening the pericardial sac, a large clot was found loosely attached to the right atrium just above the atrioventricular groove. A shallow groove was also present over the right ventricular musculature. There was no damage done

From the Departments of Surgery, Anesthesiology and Medicine, Bella Vista Hospital, Mayagüez, Puerto Rico.

to the coronary vessels. Examination of the atrium disclosed the presence of a stellate laceration with ragged edges which was filled by a large clot that extended into the right pleural cavity. Relatively free drainage had been accomplished through the pericardial perforation thereby avoiding pericardial tamponade. After exclusion of the lacerated portion of the atrium with a Satinsky clamp it was easy to resect the torn edges and effect closure using braided silk sutures. Bleeders and air leaks from the lung and intercostal vessels were appropriately treated until hemostasis was accomplished. The pericardium was loosely closed leaving a draining site into the right pleural cavity, anterior and posterior chest tubes were left in situ, and the chest wall was closed in the conventional manner. The post-operative course was uneventful except for isolated episodes of profuse sweating which, at the time, suggested hypovolemia. A pericardial friction rub disappeared on the fifth post-operative day.

An electrocardiogram taken on the second post-operative day revealed abnormal ST and T wave changes, nonspecific, compatible with postero-inferior wall damage. Another electrocardiogram taken 6 months post-operatively was within normal limits.

During the operative procedure and the first post-operative day a total of 4.5 L of blood were given. The patient kept his vital signs within the normal range except for a persistent tachycardia which spontaneously subsided during the first week. Serial chest X-rays, at appropriate intervals, showed slow resolution of the pulmonary hematoma with eventual disappearance in about 6 weeks. A month after discharge the patient was re-admitted complaining of shortness of breath, fever and slight cough. Dullness to percussion at the right base and decreased breath sounds were evident. The temperature was 101º F. Chest films showed a pneumonitis in the right middle and lower lobes. This responded well to antibiotics (after sputum culture) and intermittent positive pressure breathing (IPPB) using detergents and bronchodilating agents. Because of a tendency to develop episodes of fever and recurrent pneumonitis, the patient was advised to continue intermittent positive pressure breathing at home which he did for several months after discharge. When last seen in February 1966 (10 months post-operatively), the patient was under no medication and back to work. His recovery was complete.

Discussion

Gunshot wounds of the heart are usually fatal. The development of cardiac tamponade, conduction disturbances or damage to coronary vessels, together with the associated hemorrhage, are limiting factors that may prevent these patients from receiving necessary surgical treatment at the appropriate time. Under such life threatening circumstances, fast and smooth decisions can mean the difference between success and failure. While prompt surgical exploration, in our opinion, is the method of choice in the vast majority of these cases, mature judgement when dealing with these lesions is essential and has no substitute. In no other emergency is teamwork more appreciated than in such an instance. This includes the participation of alert and responsible nurses and well qualified medical and paramedical personnel. Although surgical treatment should be prompt, and there is no time for delay, the surgeon must try if at all possible, to screen the extent of the damage. We use the word "screen" because often an exact diagnosis cannot or need not be made prior to surgery but it is essential to know if the damage is limited to one hemithorax or if there is a concomitant contralateral preumohemothorax. Lack of this knowledge can lead to hasty surgery that may result in cardiac arrest with discovery of the cause for the complication at the autopsy table. We are well aware that the treatment of heart wounds is a controversial subject; however, we feel that any suspected wound of the heart should have

the benefit of surgical exploration. Conservative groups propose aspirations. These methods are not without serious risks (injury to the coronary vessels, etc.) and frequently fail (clotted hemopericardium). With the recent advances in the field of cardiovascular and thoracic surgery, exploration is by far the lesser of evils.

Summary

A case of a gunshot wound of the chest perforating the right middle lobe and the right atrium has been presented. Emergency surgical exploration was promptly undertaken and, together with adequate blood replacement, and appropriate post-operative measures, resulted in full recovery. Considerations regarding the management of these wounds have been discussed.

Resumen

La supervivencia subsiguiente a heridas por arma de fuego que lesionan el corazón es relativamente rara debido a numerosos factores y circunstancias que juegan un papel decisivo en el desarrollo de los acontecimientos que van unidos a este tipo de lesiones.

Un caso de herida de bala afectando el pulmón y aurícula derecha ha sido presentado y sus aspectos generales discutidos.

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EDITORIAL

EL NUEVO SECRETARIO DE SALUD

Es motivo de satisfacción para la Asociación Médica de Puerto Rico y para la Junta Editora del Boletín, la noticia sobre la selección del doctor Mario R. García Palmieri como nuevo incumbente de la Secretaría de Salud.

Graduado de Bachiller en Ciencias de la Universidad de Puerto Rico y de la Escuela de Medicina de la Universidad de Maryland, el doctor García Palmieri recibió su entrenamiento postgraduado en el Hospital de Distrito de Bayamón, el Hospital de Veteranos y la Escuela de Medicina de Puerto Rico. En años siguientes fue certificado por el "American Board of Internal Medicine" y el "American Board of Cardiology". En 1955 *se unió a la Facultad de Medicina Interna de la Escuela de Medicina, asumiendo la jefatura de ese Departamento en* 1961.

El doctor García Palmieri es autor de numerosos trabajos sobre esquistosomiasis y enfermedades cardiovasculares, varios de los cuales han sido publicados en el Boletín. Recientemente publicó su libro sobre electrocardiografía y vectorcardiografía en enfermedades congénitas del corazón.

Desde 1954 *el doctor García Palmieri ha sido miembro de la Asociación Médica de Puerto Rico. Ha participado activamente en nuestras actividades científicas. De* 1961 *a* 1965 *fue Presidente de la Junta Editora del Boletín, de la cual sigue siendo miembro.*

En todas sus empresas en los campos de investigación científica y en la medicina académica, el doctor García Palmieri se ha distinguido por su dedicación y entusiasmo.

La Asociación Médica y esta Junta Editora desean al nuevo Secretario de Salud los mayores éxitos en su nueva tarea de guiar el desarrollo de la medicina pública en Puerto Rico durante la presente crucial etapa de su desarrollo.

Julio V. Rivera, M. D.

NOTICIAS

Locales

BOLETINES VIEJOS

La Asociación Médica de Puerto Rico está interesada en obtener copia de los siguientes números del Boletín:

Año	*Meses*	*Año*	*Meses*
1921	enero a diciembre	1942	enero a diciembre
1922	" " "	1943	" " "
1923	" " "	1944	" " "
1924	" " "		
1925	" " "	1953	abril, junio y agosto.
1926	" " "	1956	enero a diciembre.
1927	" " "	1957	agosto.
1928	" " "	1962	julio.

Aquellos miembros de nuestra matrícula que tengan estos volúmenes y deseen donárselos a la Asociación Médica, favor de comunicarse con el Sr. Eulogio Bermúdez Velez, Secretario de Redacción.

DIVULGACION MEDICA

Sintonice nuestro programa televisado, "Divulgación Médica", por la nueva estación WITA-TV Canal 30, todos los sábados, de 5:00 a 5:30 p. m.

REUNIONES

Agosto 27.—Reunión de la Cámara de Delegados de la Asociación Médica de Puerto Rico, en Ponce, Puerto Rico.

Septiembre 4.—Día del Médico. Solicite información adicional a la Asociación Médica de Puerto Rico, teléfono 725-6969.

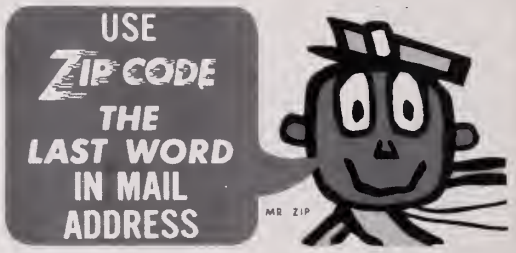
Octubre 6.—Convención de la Sección de Psiquiatría, Neurología y Neurocirugía.

Octubre 29.—Cámara de Delegados en Asociación Médica de Puerto Rico.

Octubre 31.—Convención Anual de la Sociedad Americana de Medicina Tropical e Higiene, en el Hotel Americana.

Noviembre 15-19.—Asamblea Anual Asociación Médica de Puerto Rico, Hotel San Juan, San Juan, Puerto Rico.

Noviembre 21-25.—8:00 p. m.— Conferencia por el Dr. Albert Montgomery Kligman auspiciada por el "American Academy of General Practice" y la Sección de Medicina General de la AMPR, en los salones de la Asociación Médica de Puerto Rico.



EXAMEN SEROLOGICO ESPECIFICO PARA SIFILIS Y SERVICIO DE MICROSCOPIO A CAMPO OSCURO

Ha llegado a conocimiento del Programa de Control de Enfermedades Venéreas así como al Instituto de Laboratorios de Salud Pública el hecho de que muchos médicos necesitan disponer de un examen serológico para sífilis más específico que el VDRL cuando se encuentran con casos atípicos.

El Instituto de Laboratorios de Salud Pública está equipado para procesar el "Reiter Protein Complement Fixation (RPCF)" y el "Fluorescent Treponemal Antibody (FTA)" en cantidad limitada y cuando éstos sean requeridos. El Instituto puede además requerir del "Venereal Disease Research Laboratory" en Atlanta, Georgia, la prueba "Treponema Pallidum Inmobilization (TPI)" cuando sea necesario.

Al someter una muestra de sangre para el "FTA" o para el "RPCF" se debe marcar en el parte de remisión como sigue: *Special STS-att. J. L. Villamil, M. D.* De ocho a diez cc de sangre serán necesarios para estos análisis. Se debe acompañar la muestra de sangre de un historial completo del caso con resultados de serologías anteriores y actuales. Los resultados de estas pruebas serán devueltos

a la oficina del médico en el término de una semana.

Los servicios de microscopio de campo oscuro están disponibles en toda la isla. Cualquier médico interesado en estos servicios puede llamar a la Sección de Control de Enfermedades Venéreas del Departamento de Salud (723-2612) *collect* donde se harán arreglos para este servicio.

Nacionales

STUDY ON THE COST OF DRUGS

This study has focused primarily on the cost of prescription drugs, and on various methods of reducing their unit costs so that appropriate drug therapy may be made available to many more of those who need it and now do not get it. At the same time, it has been recognized that the greatly increased investment of both public and private funds in drug therapy in recent years has been directly related to the remarkable progress in the control of disease, the improvement in health, and the lengthening of life in this country and throughout the world.

Recent legislation has been noted which strengthens governmental controls of the manufacture and sale of drugs, and grants new authority for requiring that drug preparations be effective as well as safe for their advertised uses. Other official bodies that evaluate safety and efficacy of prescription drugs have been described, together with a number of other sources of drug information widely used by the medical profession. Note has also been taken of the reliance of many physicians upon the advertising and other promotion methods of the drug manufacturer, the protection which the patent laws provide manufacturers, and the contribution of these factors to the prescribing of expensive drug preparations.

It has been proposed that the Welfare Administration consider limiting payment for drug prescriptions from public funds which it administers to those which are prescribed by a drug's generic name only. The assumption behind this proposal is that the pharmacist who fills such prescriptions would fill them from the least expensive of competing preparations of that drug. This proposal has been analyzed but not recommended.

In its place, on the basis of an official statement issued jointly by the American Medical Association and the American Public Welfare Association, the following recommendation is made: Since the prescribing physician must take the responsibility for the treatment of his patient, he should have the right to select the drugs which he prescribes, but this right should be exercised with "emphasis on the use of U.S.P., N.F., N.N.D., and A.D.R. (*U.S. Pharmacopeia, National Formulary, New and Nonofficial Drugs, and Accepted Dental Remedies*) counterpart drugs of equal therapeutic effectiveness when available, when the quality of the product is assured, and when a price differential exists."

There have been various methods of drug management developed in this country and abroad which have been directed at economy consistent with effectiveness of patient treatment and recognition of professional prerogatives. A discussion has been included of the hospital formulary, the Veterans Administration Hometown Medical Care Program, bulk purchases by large users through competitive bids, operation of pharmacies by groups such as labor unions and the Association of Retired Persons, and efforts to hold down drug costs by group health and Blue Cross agencies. The experience of foreign programs has also been cited, particularly methods used by the General Medical Service of Scotland and by the National Health Service in England and Wales.

From the point of view of the Welfare Administration, an analysis has been made of the experience of several State agencies in the management of drugs in public assistance, and a proposal offered of a method of cost economy believed consistent with the principles of the joint AMA-APWA guides and of the Welfare Administration.

To give an indication of the context of drug cost problems, some of the larger areas of unmet need in the entire field of public medical care have been briefly reviewed. This unmet need was found to be greatest among those needing treatment in the community outside of the hospitals and other institutions where the more successful measures of

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Reproduced from: Study of Drug Purchase Problems and Policies, Welfare Research Report 2, U.S. Department of Health, Education, and Welfare, Welfare Administration, Division of Research, Washington, D. C.

drug price control have been available. The inadequacy of present public assistance provisions for medical care and treatment of recipients in their homes is a major problem for the Welfare Administration. It emphasizes the appropriateness of the Welfare Administration's concern for holding unit drug costs to the minimum consistent with efficacy, so that assitance funds may stretch farther.

This agency is equally concerned about the many poor of all ages who are managing without public assistance but are without needed medicines because they cannot afford them. Section V describes various methods by which low-income persons can participate in group approaches to the control of drug costs, but the great majority of persons for whom governmental or charitable medical care is not available are dependent upon their private physician's prescribing habits for moderation in the cost of the drugs they need.

The need for this report has arisen from recent extensions of the responsibilities of the Welfare Administration in the field of medical care. Its purpose is to give a clearer picture of what can be accomplished in the control of drug costs within the sphere of influence of the Welfare Administration.

The ultimate control of the cost of drugs, however, lies in the hand of the physician who writes the prescription.

BED WETTING

Bed wetting on the part of older children is a nuisance problem that plagues untold American families.

Bed wetting is messy for the parents, who have to clean it up. It is uncomfortable and humiliating for the child. And it can be very difficult to stop.

One of hundreds of letters on this theme received annually by Today's Health, the magazine of the American Medical Association, begins: "I have four children, ages nine, seven, five and four, who have never achieved the ability to stay dry at night. All still have occasional accidents during the day."

At least two separate studies in hospital clinics, says Today's Health, revealed that incidence of bed wetting among 1,000 patients over five year old was as high as 25 per cent. Also, there is evidence from several studies that bedwetting can be a hereditary as well as a psychological problem.

The parent is advised to explore with the physician the various means that might be taken to train the children —either to enlarge their bladder capacity so they could go through the night, or to respond to the feeling of fullness and wake up before wetting the bed.

Several possibilities exist: use of drugs to relax the bladder; use of salty foods at bedtime to cut down urine secretion; training the child to voluntarily refrain from urinating for longer and longer periods.

AAP RELEASES REVISED REPORT ON CONTROL OF INFECTIOUS DISEASES

Oral poliovirus vaccine (OPV) is the most effective immunization procedure for the prevention of polio in children, and should be used in community-wide vaccination programs and for routine immunization in infancy and childhood.

This recommendation and other recommended procedures for immunization against such diseases as diphtheria, tetanus, whooping cough, measles and smallpox appear in the newly-revised 15th edition of the *Report of the Committee on the Control of Infectious Diseases,* released by the American Academy of Pediatrics.

The report, also called the *Redbook,* point out that inactivated polio vaccine (IPV) is also effective, (but that evaluation reveals a clearcut superiority of oral polio vaccine "from the point of view of ease of administration, immunogenic effectiveness, protective capacity, and potential for the eradication of poliomyelitis."

The *Redbook* emphasizes the need for initiation of immunization procedures against diphteria, pertussis (whooping cough) and tetanus at between 2 and 3 months of age.

Three doses of DTP vaccine (diphteria and tetanus toxoids and pertussis) should be administered at 4 to 6 week intervals, with simultaneous administration of monovalent or trivalent oral polio vaccine, the reports states.

A fourth dose of DTP and trivalent oral polio vaccine should be given one year later, and another dose of DTP should be administered at 3 years of age. The pertussis vaccine is then eliminated, and

tetanus diphtheria boosters are repeated at 6 and 12 years.

The report also recommends that children ready to enter school should again receive a single dose of trivalent polio vaccine.

Initial vaccination against smallpox should be administered sometime between 15 and 18 months during a relatively cool season the report indicates, and should be repeated at ages 6 and 12.

The report lists five schedules of measles immunization, emphasizes the greather effectiveness of the live virus vaccines, and recommends that all infants receive measles vaccine "by the end of the first year of life."

Children should be tested for tuberculosis at between 9 and 11 months of age, and should be tested annually until age 4, and thereafter every two years, the report states. Also, TB tests should be given before the administration of measles vaccine.

The *Redbook* contains a completely rewritten section on the use and abuse of immune serum globulin, an updated section on immunization requirements for foreign travel, a completely new section on parasitic diseases, and a revised and updated section on drugs dosages.

Copies of the *Redbook* may be obtained from Academy Headquarters, 1801 Himman Avenue, Evanston, Illinois 60204. Price is $1.50.

AMERICAN COLLEGE OF PHYSICIANS POST GRADUATE MEETINGS

Sept. 28-*Oct.* 1 Advances Incutaneous Medicine, Rochester, Minn.
Oct. 3-7 The Care of the Critically ill Medical Patient, Syracuse, N.Y.
Nov. 7-11 Endocrine And Metabolic Disorders, Brooklyn, N.Y.
Nov. 14-18 Newer Aspects of Experimental and Clinical Allergy, Boston, Mass.
Nov. 28-*Dec.* 2 Progress in Gastroenterology-1966, Philadelphia, Pa.
Dec. 5-9 What the Internist Should Know About Cancer, New York, N. Y.
Dec. 14-17 Infectious Diseases, Pittsburgs, Pa.

Internacionales

Oct. 23-29—IX International Cancer Congress. Tokyo, Japan. A charter flight and several group flights are contemplated, thus substantially reducing the cost of transportation. Members of the immediate family of congress participants will be eligible. Anyone interested should communicate with Tirsch Marks, M.D., 435 East 57th Street, New York 22, N. Y.

XV CONGRESO PANAMERICANO DE TUBERCULOSIS Y ENFERMEDADES DEL APARATO RESPIRATORIO

Oct. 24-28—XV Congreso Panamericano de Tuberculosis y Enfermedades del Aparato Respiratorio, en Buenos Aires, organizado por la Unión Latinoamericana de Sociedades de Tisiología y auspiciado por la Comisión Nacional Ejecutiva del Sesquicentenario del Congreso de Tucumán y de la Declaración de la Independencia.

Las sesiones científicas tendrán lugar en la Academia Nacional de Medicina, y el Comité Organizador, que preside el doctor Raúl F. Vaccarezza, ha fijado los siguientes temas:

I. Profilaxis de la tuberculosis: quimioterapia, vacunación y quimioprotección.
II. Resultados del tratamiento en las recrudescencias, recaídas y cronificación de la tuberculosis pulmonar.
III. Micosis broncopulmonares.
IV. Cáncer de pulmón: Diagnóstico y condiciones de operabilidad.

Los temas Profilaxis de la tuberculosis y Micosis broncopulmonares serán desarrollados en simposios y los dos temas restantes con presentación de relatos y comunicaciones.

La Secretaría del Congreso funciona en José Andrés Pacheco de Melo 3081.

Instrucciones para los Autores:

El Boletín acepta para su publicación artículos relativos a medicina y cirugía y las ciencias afines. Igualmente acepta artículos especiales y correspondencia que pudiera ser de interés general para la profesión médica.

El artículo, si se aceptara, será con la condición de que se publicará únicamente en esta revista.

Para facilitar la labor de revisión de la Junta Editora y del impresor, se requiere de los autores que sigan las siguientes instrucciones:

a) Los trabajos deberán estar escritos a máquina a doble espacio y por un solo lado de cada página, en duplicado y con amplio margen.

b) En página separada debe incluirse lo siguiente: título (no excediendo de 80 letras y espacios), nombre del autor (es), institución y dirección postal del autor.

c) Artículos referentes a resultados de estudios clínicos o investigaciones de laboratorio deben organizarse bajo los siguientes encabezamientos: (1) introducción, (2) material y métodos, (3) resultados, (4) discusión, (5) resumen (en español e inglés), y (6) referencias.

d) Artículos referentes a estudios de casos aislados deben organizarse en la siguiente forma: (1) introducción, (2) observaciones del caso, (3) discusión, (4) resumen (en español e inglés), (5) referencias.

e) Las tablas, notas al calce y leyendas deben aparecer en hojas separadas.

f) Si un artículo ha sido leído en alguna reunión o congreso, así debe hacerse constar como una nota al calce.

g) Deben usarse los nombres genéricos de los medicamentos. Podrán usarse también los nombres comerciales, entre paréntesis, si así se desea.

h) Se usará con preferencia el sistema métrico de pesos y medidas.

i) Las fotografías y microfotografías se someterán como copias en papel de lustre sin montar. Los dibujos y gráficas deben prepararse a tinta negra y en papel blanco. Todas las ilustraciones deben estar numeradas (números arábigos) e indicar la parte superior de las mismas. Debe escribirse una leyenda para cada ilustración.

j) Las referencias deben ser numeradas sucesivamente de acuerdo con su aparición en el texto. Los siguientes ejemplos pueden servir de modelo:

6. *Koppisch, E.* Pathology of arteriosclerosis. Bol. Asoc. Med. P. Rico 46: 505, 1954. (artículo de revista).
4. *Wintrobe, M. M.* Clinical Hematology, 3rd Ed. Lea and Febiger, Philadelphia, 1952, p. 67. (libro).

Deben usarse solamente las abreviaturas indicadas en el Cumulative Index Medicus que publica la Asociación Médica Americana.

Instructions to Authors:

The Boletín will accept for publication contributions relating to the various areas of medicine surgery and allied medical sciences. Special articles and correspondence on subjects of general interest to physicians will also be accepted. All material is accepted with the understanding that it is to be published solely in this journal.

In order to facilitate review of the article by the Editorial Board and the work of the printer, the authors must conform with the following instructions:

a) The entire manuscript, including legends and references, should be typewritten double-spaced in duplicate with ample margins.

b) A separate title page should include the following: title (not to exceed 80 characters and spaces), author's name (s); institution, and author's mailing address.

c) Articles reporting the results of clinical studies or laboratory investigation should be

organized under the following headings: (1) introduction, (2) material and methods, (3) results, (4) discussion, (5) summary in English and Spanish, (6) references.

d) Case reports will include (1) introduction, (2) description of the case, (3) discussion, (4) summary in English and Spanish, (5) references.

e) Tables, footnotes and legends to figures should appear in separate sheets.

f) If the paper has been presented at a meeting, the place and date should be stated as a footnote.

g) Generic names of drugs should be used. Trade names may also be given in parenthesis, if desired.

h) Metric units of measurement should be used preferentially.

i) Photographs and photomicrographs should be submitted as glossy prints, unmounted. Drawings and graphs should be made in black ink on white paper. All illustrations should be numbered (Arabic) and the top indicated. A legend should be given for each.

j) References should be numbered serially as they appear in the text. The following form will be used:

6. *Koppisch, E.* Pathology of arteriosclerosis. Bol. Asoc. Med. P. Rico 46: 505, 1954. (for journal articles).
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Abreviations will conform to those used in the Cumulative Index Medicus, published by the American Medical Association.

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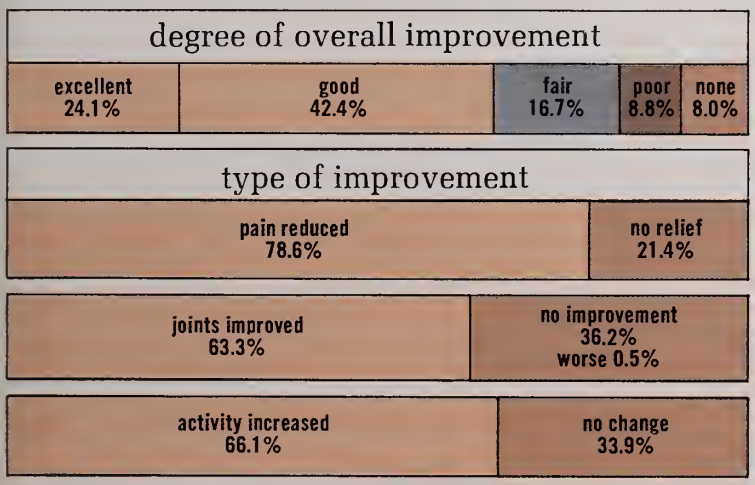

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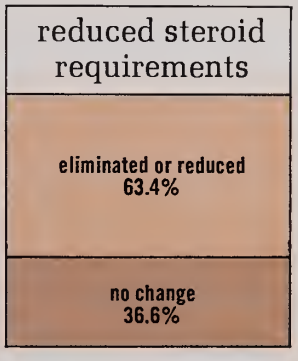
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RESUMEN: ACCION E INDICACIONES: Una sola dosis de IMFERON (inyección de hierro dextrán) produce una alza apreciable de la hemoglobina y una serie completa de inyecciones restituye efectivamente los depósitos de hierro. El IMFERON está indicado únicamente en casos diagnosticados de anemia ferropriva, en los que resulta inefectiva o poco práctica la administración de hierro oral. Tales deficiencias de hierro pueden incluir: pacientes en el último trimestre de gestación; pacientes con trastornos gastrointestinales o en vías de recuperación de intervenciones quirúrgicas del tracto gastrointestinal; hemorragias crónicas con pérdidas de hierro continuas y masivas que no responden rápidamente al hierro oral; pacientes refractarios a transfusiones como fuente de hierro; niños con anemia hipocrómica; pacientes en quienes no se puede confiar que tomen hierro oral.

COMPOSICION: El IMFERON (inyección de hierro dextrán) es una solución bien tolerada de complejo de hierro-dextrán que proporciona el equivalente a 50 mg. de hierro elemental por cada cc. La solución contiene 0.9% de cloruro de sodio y su pH varía entre 5.2 y 6. El frasco-ámpula de 10 cc. contiene 0.5% de fenol como preservativo.

ADMINISTRACION Y POSOLOGIA: La dosis, basada en el peso corporal y gramos de hemoglobina en 100 cc. de sangre, varía desde 0.5 cc. para lactantes hasta 5 cc. para adultos, aplicada diariamente, en días alternos, o semanalmente. El requerimiento total en cada individuo es fácilmente determinado mediante la tabla de dosificación contenida en el prospecto. La inyección intramuscular profunda en el cuadrante superior externo de la región glútea, empleando la técnica trayectoria en Z (con desplazamiento lateral de la piel, previo a la inyección), asegura buena absorción y evita la coloración de la piel. Se recomienda una aguja de por lo menos dos pulgadas de largo para el adulto normal.

EFECTOS SECUNDARIOS: La incidencia de efectos secundarios sistémicos y locales es poco común. Puede ocurrir coloración de la piel. Una dosis excesiva, superior a la requerida, puede producir hemosiderosis. A pesar de que las reacciones alérgicas o anafilácticas son rarísimas, se han presentado ocasionalmente reacciones serias; tres reacciones fatales han sido atribuidas al IMFERON (inyección de hierro dextrán). Raras veces se ha reportado urticaria, artralgia, linfoadenopatía, náusea, jaqueca y fiebre. Se recomienda aplicar inicialmente una dosis de prueba de 0.5 cc.

PRECAUCIONES: Si hay reacción de sensibilidad a la dosis de prueba no deberá administrarse el fármaco. El IMFERON (inyección de hierro dextrán) deberá administrarse únicamente por vía intramuscular profunda. La inyección deberá solamente aplicarse en el cuadrante superior externo de la región glútea, y no en el brazo u otras áreas. El riesgo de carcinogénesis en seres humanos es insignificante cuando se emplea el IMFERON (inyección de hierro dextrán) en la forma recomendada.

CONTRAINDICACIONES: El IMFERON (inyección de hierro dextrán) está contraindicado en pacientes con sensibilidad comprobada al complejo de hierro dextrán. Por estar destinado exclusivamente a la terapia de las anemias ferroprivas, no deberá utilizarse en el tratamiento de otras anemias.

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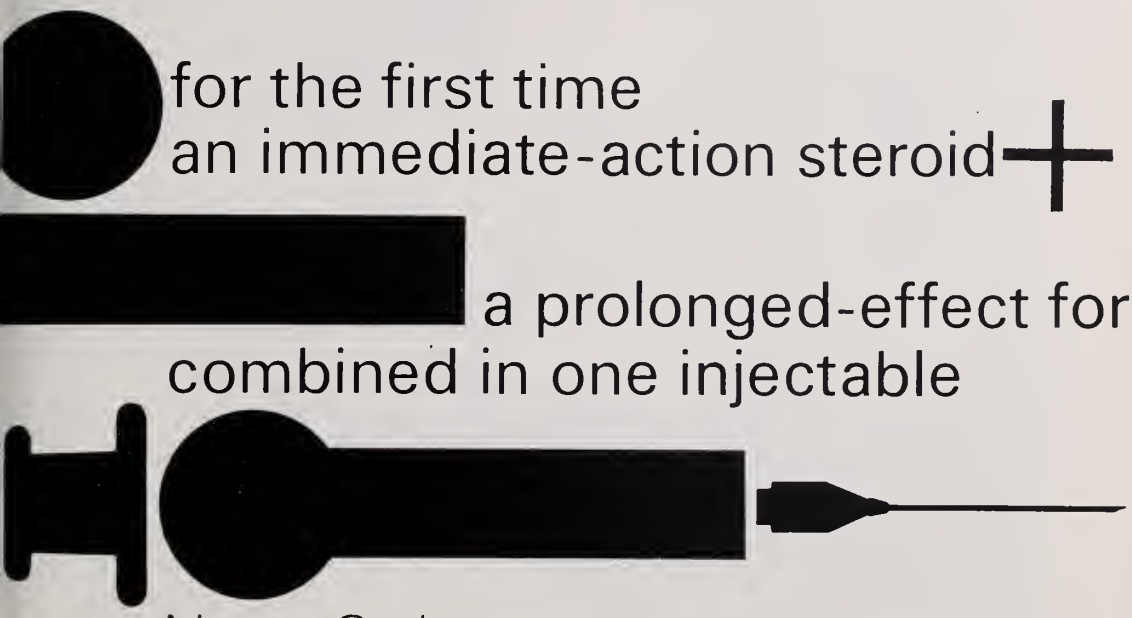
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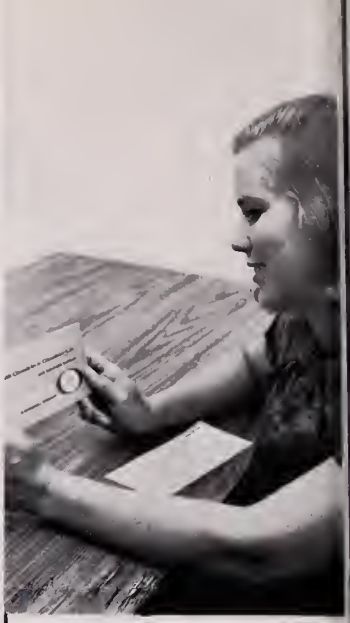
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*Crawford, L. V., et al.: Ann. Allergy *23*:303 (July) 1965.

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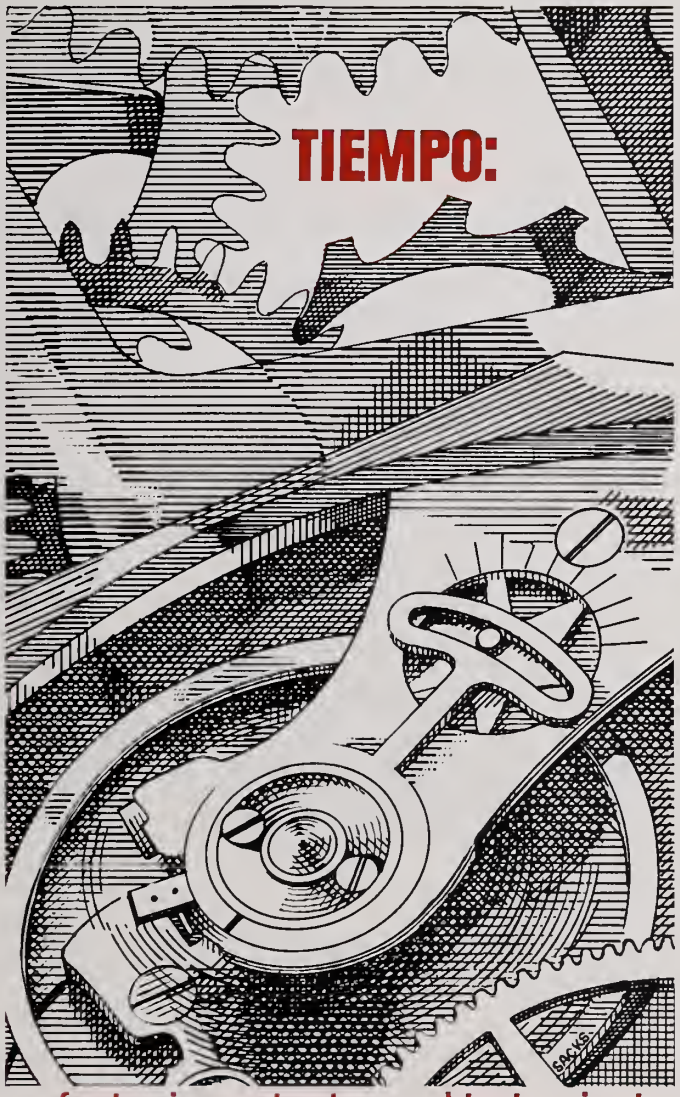
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TREATMENT OF DIGITALIS INTOXICATION: A REVIEW

J. M. Torres Gómez, M. D., F. A. C. P.

Digitalis intoxication is one of the most important of iatrogenic diseases. It must be considered a serious cardiac emergency when it causes ectopic arrhythmias, conduction defects, and suppression of sinus pacemaking function. Potassium wastage induced by diuretics, advanced age, and severe longstanding congestive heart failure cut further into the narrow margin of safety of digitalis. For these reasons, great efforts have been made to find the effective neutralizer of its toxic reactions. However, up to the present time there is no single therapeutic modality that we can rely upon for adequacy. We sill have a lot of therapeutic juggling to do if we wish to control quickly and effectively the undesirable actions of digitalis.

Once the diagnosis of digitalis intoxication is made, administration of the drug should be stopped immediately. Even when toxicity is only suspected it is generally safer to stop the drug temporarily. However, this is often insufficient since the effects may last for days following the last dose, especially when the responsible glycoside has a slow dissipation rate. For instance, I have seen nodal rhythm resulting from digitalis intoxication persist for weeks after the drug was discontinued and after all other toxic manifestations had disappeared. We need to counteract the persistent effects of digitalis before a fatal arrhythmia ensues. Though this is not easy to accomplish, a few measures have proved beneficial.

First, a mild sedative is indicated in order to relax the patient. Diuretics, if being given, should also be stopped since, through their use, potassium is lost in the urine. Previously it was thought that the toxic effects that occurred during vigorous diuresis were due to the mobilization of the edema fluid containing digitalis. However, this theory has been discarded since the concentration of the drug in edema fluid is too low to account for digitalis poisoning (1). It seems that, instead, the loss of potassium in the urine leading to a hypokalemic state is the factor responsible for the development of toxicity.

The benefits of potassium salts in the control of ectopic cardiac rhythms have long been known. They have also been found of value in reducing myocardial irritability secondary to potassium depletion by digitalis. Intravenous potassium chloride has reversed digitalis-induced arrhythmias; however, we must be cautious in those arrhythmias associated with delayed conduction in the presence of a normal serum potassium, since potassium may increase

the block in these cases (2). Even sinus arrest has occurred following its use. But, overall, potassium is probably our most valuable tool at present in the treatment of digitalis intoxication.

Potassium is usually given orally as the chloride. The dose is one gram four times a day whether in solution or tablet form. It is perhaps better to give it in solution since, in the recent past, ulcerative lesions in the gut have been found in patients receiving potassium tablets. However, the solution has a drawback: a very repugnant taste. Though it has been attempted to improve its palatability through the addition of other chemical constituents, the patients usually complain of symptoms compatible with gastritis and not many tolerate the medicine for prolonged periods. For this reason, potassium is frequently given to these patients as the gluconate (Kaon Elixir 20 cc four times a day) although it must be understood that the chloride in the treatment of choice in view of the frequently associated finding of chloride deficit. Yet, when the deficit is of such a nature that chloride therapy is necessary, it is perhaps best corrected through the intravenous route. In these instances potassium chloride should be given intravenously but always slowly and well diluted so that cardiac arrest in diastole does not occur. Twenty milliequivalents of potassium chloride may be given in 500 ml of fluid. Of course, one must be aware of the dangers inherent in the administration of intravenous fluids to patients with congestive heart failure.

It is not always necessary to give potassium in the drug form. There are foods with high potassium content with which one can correct a body deficit adequately. Among these are meat broth, orange juice, bananas and oatmeal. When these foodstuffs are incorporated daily in the diet of a cardiac patient, potassium depletion is usually prevented in the average uncomplicated case.

Intravenous glucose-insulin solutions are of value in directing potassium back into the muscle cell. However, this type of treatment has not found wide acceptance. Probably one reason is that many of the intoxicated cases are in chronic advanced failure and, therefore, it is not wide to increase the intravascular volume.

Procaine amide (Pronestyl) and quinidine have been used in the treatment of arrhythmias due to digitalis intoxication but their use has been of limited value. Premature ventricular beats are controlled at times with these drugs and they have been used with success in both supraventricular and ventricular tachycardias caused by digitalis (3). Yet, the use of these drugs is sometimes hazardous, especially when atrioventricular conduction is delayed. Deaths have occurred after quinidine was given intravenously to patients with digitalis induced ventricular tachycardia.

Intravenous magnesium sulfate has been used to control ectopic beats, bigeminy, and ventricular tachycardia because of its depressant action on myocardial conduction and irritability. However, its effect is very transient, and at times, the underlying disturbance has been increased (1).

The successful use of sodium diphenylhydantoin (Dilantin) in the treatment of ventricular tachycardia due to digitalis intoxication has been reported recently (4,5).

It has also been used to avoid recurrences of paroxysmal atrial tachycardia. It probably has a direct effect on the myocardium and it is known to reduce the concentration of intracellular sodium. By inference, it is presumed that the concentration of intracellular potassium increases. This may explain its anti-arrythmic action. The drug is given intravenously, very slowly, under electrocardiographic control, and at a rate of 1 mgm/kg/min. If given too rapidly, it may cause respiratory or cardiac arrest.

Citrate salts, ethylenediaminetetraacetic acid (EDTA), and disodium versenate (Na_2 EDTA) constitute a group of chemical agents that act through the binding of the ionizable calcium. Digitalis excess and the serum calcium ion seem to alter the cell membrane permeability so that a blocking effect is created, preventing potassium from entering the cell. By binding the calcium in the serum this blocking effect is lessened and potassium is then allowed to move inward. EDTA and disodium versenate remove calcium from the serum by chelation. The citrate salts can also be considered chelating agents in the biological sense, since they combine with the calcium to form stable soluble complexes that are later excreted in the urine. The three drugs are effective in eliminating arrhythmias induced by digitalis. However, the effect of EDTA and the citrates is very transient and the arrhythmias return until the excess digitalis is either excreted or metabolized. Disodium versenate is too toxic for clinical use (6,7,8,9,10,11,12).

Pronethalol (nethalide) is a beta-adrenergic blocking drug that is believed to act through the interruption of cardiac sympathetic stimuli. It has also been found to limit the depletion of intracellular potassium produced by a cardiac glycoside in dogs. Because of these two properties, it was tested in digitalis-induced arrhythmias and was found to be effective in converting bigeminy, multifocal premature ventricular contractions and atrial tachycardia with block (13). It is a promising drug but still in the experimental stage. Since it appears to have carcinogenic properties, its use is not recommended for prolonged treatment. For these cases, Propanolol may be the answer in the future.

Ryanodine is a water-soluble alkaloid isolated from a plant. It has a specific suppressive action on ventricular pacemakers induced by digitalis but its negative inotropic effect and its chronotropic action render the drug too toxic for clinical use (14).

Estradiol has an effect contrary to the one of digitalis (15). It also inhibits the effects of hyperkalemia and improves the electrocardiographic abnormalities that the latter produces but apparently has not had clinical acceptance.

Paired electrical stimulation may prove useful in selected clinical situations in suppressing arrhythmias caused by digitalis intoxication. The technique consists of delivering two stimuli to the heart through an intravenous pacing catheter timed so that the second of each pair is applied at the end of the first refractory period. The result is a second depolarization without an effective contraction, i.e., a single systole for every two depolarizations, thus slowing the heart rate. However, because of the possible risk of provoking ventricular fibrillation, clinical trials of this technique may not be justified except when conventional methods of treatment have completely failed in critical cases (16).

Though manifestations of intoxication in digitalized patients have been recently observed following conversion with direct current countershock (17), a case of paroxysmal atrial tachycardia with block secondary to digitalis that responded very well to countershock conversion has also been recently reported (18). It may be worth trying in selected cases.

Summary

A partial review of the recent literature on the treatment of digitalis intoxication is presented. Though many drugs have been tested, discontinuation of digitalis and the administration of potassium are at present the most dependable and effective measures. Yet, even potassium therapy carries with itself considerable hazard in cases exhibiting conduction defects. Dilantin has a promising future.

Resumen

Se presenta un repaso de algunos datos de reciente publicación en la literatura médica sobre el tratamiento de intoxicación por digital. A pesar de que han sido muchas las drogas probadas, la descontinuación del digital y la administración de potasio siguen siendo las medidas más confiables y efectivas. Aún así, el uso del potasio conlleva sus peligros en aquellos casos que demuestran defectos de condución. El Dilantin tiene un futuro prometedor.

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CASE REPORT

CEREBRAL MUCORMYCOSIS

M. Pérez Arzola, M. D.
M. García Soria, M. D.
Edwin Rivera, M. D.

Disease of a serious prognostic nature produced by fungi of the order *Mucorales* has been recognized since 1885 (1) and is becoming more prevalent as judged by the frequency of reports in recent medical literature. Since the report of Gregory and coworkers in 1943 (2) special attention has been given to the association of mucormycosis with diabetes mellitus, but more recently it has been reported in conjunction with other debilitating conditions or superimposed on other bacterial infections. The *Mucorales,* it has been established pretty definitely, are invaders of tissues previously affected by disease and very rarely are primary pathogens. In non-diabetic subjects conditions which seem to predispose the patient to the development of mycormycosis include blood dyscracias (especially leukemia and multiple myeloma), terminal carcinomatosis, tuberculosis, cirrhosis, hepatitis, extensive burns, pyelonephritis, septicemia and the use of certain drugs like folic acid antagonists, antibiotics and cortisone. Whereas the diabetic affected with this condition is more susceptible to develop brain involvement (two thirds of the cases in Mc Bride's review of the literature) (3), pulmonary, gastrointestinal and disseminated involvement seems to be more frequent in the non-diabetic.

A case of mucormycosis with brain involvement was recently identified at the Ponce Municipal Hospital. It is our purpose to present the clinical and pathological aspects of this patient, probably the first case of mucormycosis reported from Puerto Rico, and to discuss briefly the pathogenesis, diagnosis and management of this usually fatal condition.

Case Report

This 43 yrs. old white male had been a known mild diabetic for the past 2 years, apparently well controlled on diet. He had been in a fairly good state of health until 2 days prior to admission when he started to develop polyuria, polydypsia, low grade fever and nausea. On the day of admission the patient noticed redness and pain in his left eye along with difficulty focusing and ptosis of the left eyelid. This was accompanied by cephalalgia and some drowsiness.

On physical examination we found the patient looking acutely ill and somewhat drowsy but answering questions coherently. Blood pressure was 150/90 mm Hg, temperature 100°F, pulse 86/min, respirations 22/min. The rest of the physical examination was negative except for ptosis of the left eyelid, marked redness of the left conjunctiva and paralysis of the left lateral rectus ocular muscle.

Laboratory studies on admission revealed a hemoglobin of 12.9 gm, hematocrit 39%, leukocytes,

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5750/cu. min. with 68% polys and 32% lymphs. Urine specific gravity was 1.020, 3+ albumin, 4+ sugar. Blood glucose was 398 mg%. Chest and skull X-rays were reported as negative. Sinus X-rays revealed moderate blurring of both ethmoidal and frontal sinuses indicative of sinusitis. A spinal tap revealed increased initial pressure (280 mm of water); glucose, 299 mg%, total proteins of 91 mg% and occasional erythrocytes and leukocytes. Treatment initially consisted of attempts at controlling the diabetes with crystalline and long acting insulins, diet and analgesics. One day after admission the patient presented marked swelling and proptosis of the left eyeball, left facial palsy of central origin, marked worsening of the headaches and drowsiness. At this stage and under the clinical impression that we were dealing with a case of cerebral mucormycosis the patient was started on Amphotericin B, 25 mg. diluted in 1000cc of 5% dextrose infused in a period of 6 hours. The patient kept on going downhill rapidly, however, eventually going into a deep stupor and expiring quietly 3 days after admission.

Necropsy disclosed an area of encephalomalacia measuring about 5cm in diameter localized in the left frontal lobe at the base of the brain. The underlying dura was granular and hyperemic. No abnormalities were seen in the sinuses grossly. A piece of orbital bone cultured in Sabouraud's medium revealed a rather heavy growth of a fungus which on further identification turned out to be of the genus *Rhizopus* (Figures 1, 2, 3).

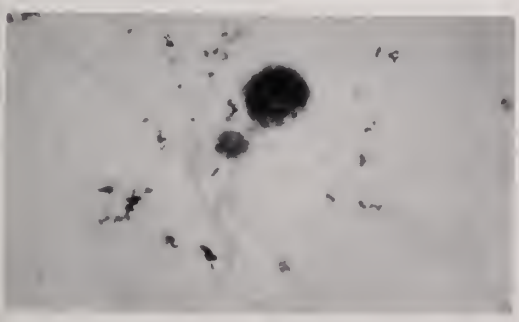


Fig. 1: Growth of *Mucorales* of the genus *Rhizopus* on Sabouraud's medium culture of a piece of orbital bone obtained on necropsy. Sporangiospores contained within sporangia as well as branching non septate hyphae are evident on this picture.



Fig. 2: Higher magnification of sporangiospores and sporangium. The rapidly multiplying spores are already breaking loose from the thick spore case.



Fig. 3: Higher magnification of the non septate hyphae typical of fungi of the order *Mucorales*.

Comments

Etiology: The infection is produced by a member of the order *Mucorales* of which three genera have been found so far to produce disease in man-*Mucor, Absidia* and *Rhizopus*. They are better known as bread or sugar fungi but are also found on other decaying vegetable matter and in the soil. Their preponderance can probably be explained by their simple requirements of sugar or carbon compounds for their nutri-

TABLE I: FREQUENCY OF VISCERAL INVOLVEMENT IN 61 PATIENTS WITH MUCORMYCOSIS

Associated Condition	Site of Involvement				
	Brain	Lung	G. I. Tract	Kidney	Disseminated
Diabetes	20	3	0	0	4
No Diabetes					
Leukemia or multiple mycloma	0	11	0	0	2
No Leukemia or multiple mycloma	4	2	4	1	10

TABLE II: AGE, RACE AND SEX IN 61CASES OF VISCERAL MUCORMYCOSIS

Diabetes	Sex		Race		Age (years)	
	Male	Female	White	Negro	Under 20	Over 20
Present (27 cases)	15	12	20	7	4	24
Not present (34 cases)	26	8	30	4	11	22

tion. The *Mucorales* grow rapidly in Sabouraud's medium and are characterized by the presence of non-motile, asexual spores (sporangiospores) contained within a spore case (sporangium). They obtain their nutrition through the rhizoids which are attached to the nutrient. The fungus is identified readily in hematoxylin and eosin or PAS-stained tissue sections by the morphology of their non-septate hyphae and by the propensity of the fungus to invade venules and arterioles and form mucorthrombi.

Infection in Man: Paltauf described the first case of human mucormycosis in 1885. This patient, who was not a diabetic, had intestinal (probable portal of entry) as well as brain, lungs, kidney and mesenteric lymph nodes involvement (1). Since then, 64 cases, including our own, have been reported in the English literature. Of these, 61 had visceral involvement. Twenty seven of the cases were proven diabetics (44%) of which 20 (74%) had cerebral involvement. Of the 34 non diabetics, 13 had either leukemia or multiple myeloma and the visceral involvement was usually pulmonary (39%) or disseminated (36%).

The case presented by Zimmerman in 1955 is particularly interesting since the cause of death was a myocardial infarction secondary to mucorthrombosis of coronary veins in a 53 years old male with multiple myeloma (4). Although there appears to be no age group or racial predilection the disease is three times as common in males as in females in the non-diabetics. In the diabetic patients there does not seen to be any sex difference in its prevalence (table II).

Why an ubiquitous and usually innocuous fungus suddenly becomes invasive and extremely virulent remains a moot question. Zimmerman considered decreased host resistance, local lesions secondary to the primary disease and metabolic alterations produced by therapeutic agents as permissive factors in human proliferation of the usually saprophytic fungus (4).

The explanation for the preponderance of cerebral lesions in the diabetic and the pulmonary or generalized forms in the non-diabetic remains also unanswered. Bauer and coworkers demonstrated the predisposition to cerebral mucormycosis in alloxan-induced diabetic rabbits given spores of *Rhizopus* intranasally (5). In the cerebral form the patient usually presents a syndrome of uncontrolled diabetes, ophthalmoplegia, meningoencephalitis and frequently purulent sinusitis, the pathological lesions being localized around the brain and eye. In these cases the fungus usually gains entrance through the upper respiratory tract, proliferates in the sinuses and eventually produces an orbital cellulitis with extension into the brain through the vascular channels or maybe via the cranial nerves. The pathological changes in the brain are on the basis of areas of infarction due to mucorthrombosis and meningoencephalitic areas in the brain substance due to direct extension.

In pulmonary involvement as discussed by Baker (6) the fungus is apparently aspirated into the bronchi and multiplies within them. Infection of the arterial walls and thromboarteritis follows, with the production of pulmonary infarcts. The penetration of thick, viable arterial walls by the fungus is a phenomenon difficult to explain in these cases.

In gastrointestinal involvement, also discussed by Baker et al (7), fungi in the intestinal lumen penetrate the bowel wall and

invade mesenteric vessels producing small infarcts and making dissemination possible. Moore *et al* in 1949 described a case of intestinal mucormycosis in a non diabetic who presented with widespread ulcerative colitis which resulted in death after perforation and generalized peritonitis (8).

In the disseminated form the portal of entry is either pulmonary or gastrointestinal.

Clinical suspicion of cerebral involvement as presented by our case should be aroused when the patient presents with diabetes, ophthalmoplegia (usually with proptosis) and neurological abnormalities suggestive of meningoencephalitis.

The laboratory diagnosis during life may be established by biopsy of the nasal or palatal mucosae and scrappings of secretions from the sinuses. All this material should be cultured on Sabouraud's medium and slides made with the proper stains. Blood cultures, although theoretically possible in the disseminated form, have not been reported so far in the English medical literature. Due to the ubiquity of the fungus care must be taken not to mistake it for the cause of actual disease when they may be only contaminants or saprophytes. Definite histological evidence of the fungus is necessary to establish the diagnosis.

Therapy: Seven patients, six of them diabetics, in whom diagnosis of mucormycosis was definitely established during life, have so far recovered. In pulmonary, gastrointestinal or disseminated mucormycosis recovery is more difficult since these forms are usually associated with disease of poor prognosis. Harris reported in 1955 a 14 years old diabetic with mucormycosis involving the palate, left eye and cranial nerves who recovered with proper control of the diabetes, potassium iodide and a vaccine prepared from the fungus growth obtained from a palatal biopsy (9). Baker reported an adult where *Rhizopus* was cultured from an acute ethmoidal sinusitis who recovered with rigid control of the diabetes (10). Mc Call and Strobos reported in 1957 a case due to *Rhizopus oryzae* in an eighteen years old diabetic producing sinusitis, orbital necrosis and probable cavernous sinus mucorthrombosis who recovered with diabetic control, Mycostatin, Parenzyme and potassium iodide (11).

Amphotericin B although promising in experimental mucormycosis in rabbits as reported by Chick and coworkers (12,13) had never been tried in humans until Prout in 1960 (14) and Hoagland in 1961 (15) used it succesfully along with extensive extirpative surgical procedures in cases of mucormycosis. Burrow in 1963 reported a 47 years old diabetic with orbital and cerebral mucormycosis with total recovery after 16 weeks of intensive therapy with Amphotericin B. (16). Contrary to the other patients who survived the disease, there was no significant residual deficit such as paresis or blindness on this patient. Our patient died shortly after the first dose of Amphotericin B. was administered, so that a proper evaluation of the drug could not be done.

Summary

A case of cerebral mucormycosis suspected clinically during life and confirmed at autopsy is presented.

The English medical literature regarding this serious disease is reviewed and the infection as seen in man, laboratory diagnosis,

pathogenesis and treatment are briefly discussed.

Clinical awareness of this condition should be aroused in a diabetic or a patient with debilitating illness presenting the triad of ophthalmoplegia, orbital cellulitis or pansinusitis and neurological signs suggestive of meningoencephalitis. The treatment should consist of rigid control of the diabetes and antifungal agents. Amphotericin B, promising in experimental animals, has proved to be effective in several cases of the cerebral form of the disease.

Resumen

Se presenta un caso de mucormicosis cerebral diagnosticado clínicamente y confirmado por autopsia. Se repasa la literatura sobre esta enfermedd y se discute el cuadro infeccioso tal como se presenta en el humano, su patogenia, diagnóstico de laboratorio y tratamiento. Debe sospecharse esta condición en todo paciente diabético o con alguna enfermedad debilitante que presente la tríada de (1) oftalmoplejia, (2) celulitis de la órbita o pansinusitis, y (3) signos neurológicos sugestivos de meningoencefalitis. El tratamiento consiste de un control adecuado de la diabetes y del uso de antibióticos para hongos tal como la amfotericina B.

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in a general hospital: Study of 88 patients.

CASE REPORT

DISSEMINATED HISTOPLASMOSIS COMPLICATING GRANULOCYTIC LEUKEMIA

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María A. Medina, M. S.
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Histoplasmosis is of frequent occurrence in eastern and central United States where it is endemic in certain areas such as the Missisippi Valley. It has been reported from 30 countries of the world and occurs in both the temperate and tropical zones (1).

The existence of histoplasmosis in Puerto Rico has been reported recently in several publications. Positive skin reactors to histoplasmin and serologic tests or both have been found among the children and adult population of Puerto Rico by Suarez and coworkers (2), and by Torres, Figueras and Sifontes (3). The fungus was isolated to the best of our knowledge by culture and animal inoculation for the first time by Torres de Blasini, et al (3) in 1957 from a 62-year old patient from Gurabo, who had a right upper lobe cavity and fibrosis radiologically. In 1954 one of us reported a case of histoplasma of the lung in a resected pulmonary segment from a continental patient from Florida (not published). The histoplasma was demonstrated in a caseating pulmonary nodule. However, the good fortune remained to Manuel A. De Jesus et al., who encountered and reported the first documented case of disseminated histoplasmosis in an autopsy of a native Puerto Rican child (4). The case concerning us is one of disseminated histoplasmosis known also as Darling's disease (reticuloendothelial mycosis), in memory of Dr. Samuel T. Darling who in 1905-1906, reported 3 fatal cases of a disease in Panama which he had studied while looking for visceral leishmaniasis in that country (5). Since then it has been found postmortem in its various manifestations with increasing frequency. We would like to present what we believe is the second proven case of disseminated histoplasmosis, in a native Puerto Rican who never had been out of the island.

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Presented before the annual Puerto Rico Regional Meeting of the American College of Physicians held on October 22, 1965.

Case Report

A 77-year old Puerto Rican male veteran from Caguas and a known case of granulocytic leukemia of approximately 21 months duration was readmitted for the fifth time to the San Juan Veterans Hospital on July 16, 1964, complaining of marked weakness, generalized pruritus, shortness of breath and fever. He had been hospitalized for similar complaints between April 2 and June 11, 1964.

Physical examination disclosed an emaciated, elderly male looking acutely ill with a blood pressure of 120/70 mm Hg., pulse 100/min. and tem-

perature 101°F. There was marked pallor of the conjunctive and oral mucosa. The skin showed a scaling brown macular rash of the chest and abdomen. There was dullness to percussion and diminished breath sounds in the right base. Coarse rales were heard over both pulmonary fields. The spleen was felt about four fingerbreadths below the left costal border. The liver was not palpable. Enlarged cervical and axillary lymph nodes were detected.

The laboratory data showed a WBC count of 40,000/cu. mm. with a differential of 10 myeloblasts, 20 myelocytes, 26 metamyelocytes, 17 segmented neutrophiles, 11 monocytes, 8 lymphocytes, 4 eosinophiles and 4 basophiles. Platelets were in the range of 18,000/cu. mm., and RBC 3.5 million, hematocrit 36% and a hemoglobin of 9.6 grams. The blood urea nitrogen was 14.5 mg% and the serum proteins 8.45 grams, 2.1 albumin, 6.2 globulin. The VDRL was nonreactive, an urinalysis showed 2+ albumin and stools were negative for ova and parasites. Sputum culture grew *Klebsiella aerobacter*.

An X-Ray of the chest (July 16, 1964) showed extensive infiltrations, apparently peribronchial, of the entire left lung field (Fig. 1). The right lung field was essentially clear. Both hila appeared prominent particularly on the left side. The findings were consistent with bronchopneumonia of the left lung. The apparent mediastinal adenopathy suggested leukemic involvement. (X-Rays of the chest on previous admission in April 2, 1964 had been negative).



Fig. 1: Chest X-Ray shows extensive peribronchial infiltrations of the entire left lung. Findings are consistent with bronchopneumonia of the left lung. Both hila appear prominent particularly on the left side (see arrow). The mediastinal adenopathy is suggestive of a leukemic involvement.

The patient was admitted with an initial impression of bronchopneumonia that was confirmed by a chest film. Treatment with tetracycline, achromycin, prednisone and fresh blood transfusions was given. He responded very well initially. The fever subsided and the patient became more active and less dyspneic. On August 28 purulent expectoration, fever and dyspnea recurred and the patient became drowsy. Tetracycline was again given. As the leukocyte count was now above 70,000/cu. mm. treatment with 6-mercaptopurine was also given. Bone marrow aspirate obtained July 30 grew *H. capsulatum* on culture. The patient's condition got progressively worse and he expired on July 31.

At autopsy the patient presented marked pallor and emaciation. The skin showed a dry macular rash in the trunk. The superficial lymph nodes were not palpable. Miliary gray nodules, 1 mm. or less in diameter, were discernible throughout the transparent pleura of both lungs. Similar miliary nodules up to 2 mm were found throughout the pulmonary parenchyma of both organs. A caseous nodule 8 mm in diameter, was encountered subpleurally in the upper portion of the superior segment of the lower lobe of the left lung. A tuberculoid acinodose sclerosing lesion 2 cm in diameter was found in the midportion of the apicoposterior segment of the right upper lobe. Touch preparations and pulmonary tissue were obtained at autopsy for staining and cultivation of *Mycobacterium tuberculosis* and fungi. There was a subdiaphragmatic abscess on the left side that contained 500 ml of a dark yellow brown fluid. The abscess was below the diaphragm limited by the spleen and had not ruptured into the left pleural or peritoneal cavities. Material from the abscess was not cultured. The spleen was found to be markedly enlarged and soft. It weighed 1600 grams. The upper pole and inferior surface of the spleen were covered by an orange-yellow shaggy fibrinous exudated as part

of the subdiaphragmatic abscess. The splenic substance was reddish gray, moist and finely nodular. The mesenteric and retroperitoneal lymph nodes were moderately enlarged and soft. The liver weighed 2590 grams; it was enlarged, soft and presented a normal lobular pattern. Tuberculoid nodules were not discernible in the liver parenchyma. The kidneys were of normal size and presented a normal appearance on the capsular surface and of the parenchyma. The heart, genital organs and endocrine glands were within the range of normal. Exposure of the cranial cavity disclosed a cystic organized subdural hematoma containing brown opaque fluid. The cerebrum was not appreciably compressed by the hematoma. Transections of the entire brain presented no abnormality.

Histologic examination of bone marrow from lumbar vertebrae showed a diffuse overgrowth of the granulocytic cell series with evidence of maturation arrest at the myelocytic level and a monocytoid tendency of myelocytes and metamyelocytes. The erythrocytic cell series were depressed. Megakaryocytes were found adequate, quantitatively and functionally. The subpleural nodule from the left lung showed evidence of caseation necrosis, deposition of calcium in the center and was enveloped by a fibrous capsule (Fig. 2). Multiple microsections from both lungs



Fig. 2.: The subpleural nodule from the left lung exhibiting caseation necrosis and deposition of calcium in the center. Nodule is enveloped by fibrous capsule. Magnification X5.

showed an alveolar granulomatous reaction, discrete and confluent comprised by histiocytes, leukemic granulocytes and plasma cells, and occasionally miliary epithelioid granulomas. The acinodose lesion from the right lung exhibited congeries of epithelioid granulomas and giant cells with caseation necrosis.

The fungus *H. capsulatum* was demonstrated with the PAS and Gomori's methenamine stain in the alveolar macrophages and epithelioid cells of the miliary granulomas (Fig. 3) and in the

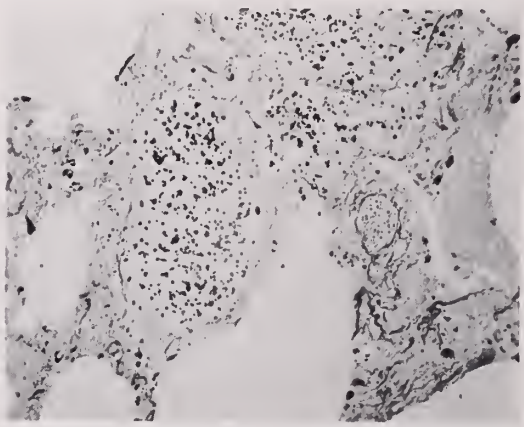


Fig. 3.: Photomicrograph of intraalveolar granulomas demonstrating *H. capsulatum* in alveolar macrophages by the Gomori's silvermethenamine impregnation. Magnification X475.

caseating primary histoplasmona of the right lung. A mucicarmine stain failed to show the microorganism in the various sections of lung. This is a point of differentiation of *H. capsulatum* from *Cryptococcus neoformas* whose capsules give a positive pink reaction. The tracheobronchial lymph nodes were infiltrated with tuberculoid granulomas comprised by epithelioid cells and giant cells of the foreign body type. Some of the granulomas showed evidence of caseation necrosis. The substance of the spleen was infiltrated with granulocytes in various stages of differentiation essentially similar to those present in the bone marrow. Megakaryocytes and nucleated red cells were also encountered with the leukemic infiltrate. The *H. capsulatum* was demonstrated in histiocytes and sinusoids of the bone marrow, lymph nodes and spleen with the Gomori's methenamine

organized under the following headings: (1) introduction, (2) material and methods, (3) results, (4) discussion, (5) summary in English and Spanish, (6) references.

d) Case reports will include (1) introduction, (2) description of the case, (3) discussion, (4) summary in English and Spanish, (5) references.

e) Tables, footnotes and legends to figures should appear in separate sheets.

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Abreviations will conform to those used in the Cumulative Index Medicus, published by the American Medical Association.

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El Boletín acepta para su publicación artículos relativos a medicina y cirugía y las ciencias afines. Igualmente acepta artículos especiales y correspondencia que pudiera ser de interés general para la profesión médica.

El artículo, si se aceptara, será con la condición de que se publicará únicamente en esta revista.

Para facilitar la labór de revisión de la Junta Editora y del impresor, se requiere de los autores que sigan las siguientes instrucciones:

a) Los trabajos deberán estar escritos a máquina a doble espacio y por un solo lado de cada página, en duplicado y con amplio margen.

b) En página separada debe incluirse lo siguiente: título (no excediendo de 80 letras y espacios), nombre del autor (es), institución y dirección postal del autor.

c) Artículos referentes a resultados de estudios clínicos o investigaciones de laboratorio deben organizarse bajo los siguientes encabezamientos: (1) introducción, (2) material y métodos, (3) resultados, (4) discusión, (5) resumen (en español e inglés), y (6) referencias.

d) Artículos referentes a estudios de casos aislados deben organizarse en la siguiente forma: (1) introducción, (2) observaciones del caso, (3) discusión, (4) resumen (en español e inglés), (5) referencias.

e) Las tablas, notas al calce y leyendas deben aparecer en hojas separadas.

f) Si un artículo ha sido leído en alguna reunión o congreso, así debe hacerse constar como una nota al calce.

g) Deben usarse los nombres genéricos de los medicamentos. Podrán usarse también los nombres comerciales, entre paréntesis, si así se desea.

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i) Las fotografías y microfotografías se someterán como copias en papel de lustre sin montar. Los dibujos y gráficas deben prepararse a tinta negra y en papel blanco. Todas las ilustraciones deben estar numeradas (números arábigos) e indicar la parte superior de las mismas. Debe escribirse una leyenda para cada ilustración.

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4. *Wintrobe, M. M.* Clinical Hematology, 3rd Ed. Lea and Febiger, Philadelphia, 1952, p. 67. (libro).

Deben usarse solamente las abreviaturas indicadas en el Cumulative Index Medicus que publica la Asociación Médica Americana.

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a) The entire manuscript, including legends and references, should be typewritten double-spaced in duplicate with ample margins.

b) A separate title page should include the following: title (not to exceed 80 characters and spaces), author's name (s); institution, and author's mailing address.

c) Articles reporting the results of clinical studies or laboratory investigation should be

silver stain. The liver sinusoids were permeated with leukemic cells. The portal spaces showed an inflammatory process with lymphocytes, plasma cells and histiocytes. Histoplasmas were demonstrated in fixed Kupffer cells, sinusoidal histiocytes and portal granulomas in the liver.

A microsection from the jejunum disclosed a histiocytic granuloma infiltrated with lymphocytes and plasma cells and the presence of histoplasma in histiocytes (Fig. 4). The kidneys showed cortical histiocytic and epithelioid granulomas. Both organs presented evidence of proximal and distal tubular necrosis and a pyelonephritic process of the right kidney. *H. capsulatum* were demonstrated in glomerular capilaries (Fig. 5) and cortical granulomas of both kidneys in the H & E and in the Gomori's methenamine silver preparation. One of the macular skin lesion from the chest showed the presence of histoplasma in a perivascular histiocytic reaction. Histoplasma were encountered in the sinusoids of the hypophysis. Granulomas were not found in the meninges or substance of the brain.

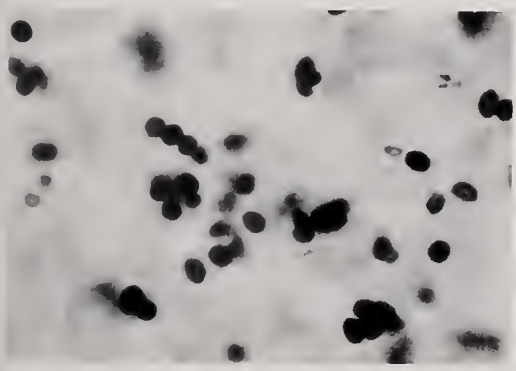


Fig. 4: Photomicrograph from granuloma of the ileum demonstrate *H. capsulatum* in histiocytes. Gomori's silver-methenamine impregnation. Budding of the yeast form of the fungus is evident. Magnification X1350.

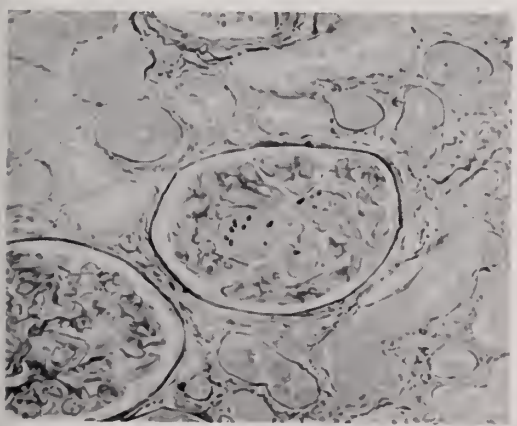


Fig. 5.: Photomicrograph from kidney. It demonstrates *H. capsulatum* in the capillaries of a glomerular tuft. Gomori's silver-methenamine stain. Magnification X475.

Mycological Study

Small oval bodies about 3 micra were observed within the cytoplasm of macrophages in touch preparations from the left lung. The organism appeared as a dark-stained eccentrically placed area surrounded by a clear halo.

Ground lung tissue was cultured in Saboraud & Mycosel agar and incubated at room temperature. In 8-10 days cottony white to brownish colonies developed. Culture mounts revealed septate, branching filamentous hyphae which support round to pyriform tuberculate chlamydospores (Fig. 6). Since the latter structures are also seen

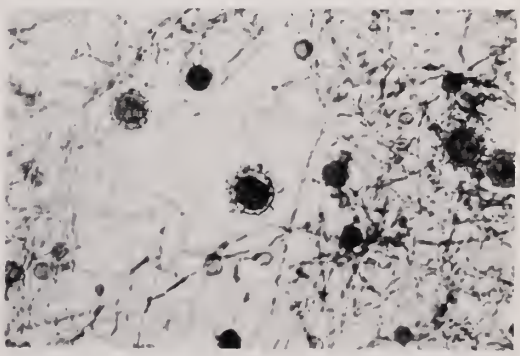


Fig. 6.: Photomicrograph of *H. capsulatum* from culture in Saboraud's glucose agar showing large, round, thick-walled, tuberculate chlamydospores. Magnification X950.

in a soil saprophyte of the genus *Sependonium*, it was essential that the mold suggestive of *H. capsulatum* be converted to yeast form in order to distinguish the pathogen from the saprophyte. *Sependonium* will not form a yeast phase. Subcultures of mycelial growth into brain heart infusion agar slants enriched with 5% defibrinated horse blood were done and incubated at 37°C (6). After 4-5 days smooth white yeast-like colonies developed. Cultured mounts revealed small oval budding cells. No mycelial elements were observed in these mounts.

A histioplasmin latex agglutinating test was performed using a serum obtained before death of the patient. In the procedure COLAB histoplasmin latex antigen was used. A 3+ titer was obtained in dilution 1:32. In the interpretation of the test a 4+ titer of 1:8 dilution is considered suggestive of active infection. Cross reaction with blastomycosis and coccidiomycosis are possible but since cultural diagnosis was established by isolation of *H. capsulatum* from lung tissue, the titer obtained is considered as having diagnostic value in this case.

Discussion

The case presented is one of disseminated histoplasmosis complicating granulocytic leukemia of 21 months duration in a 71-year old white male veteran. The portal of entry of the opportunistic fungus probably was through the respiratory tract and the pathologic evidence of this assumption was corroborated by the subpleural caseating nodule encountered in the left lung. *H. capsulatum* in its yeast form was demonstrated in touch preparations from the caseating pulmonary nodule and tissue cultures from other portions of lungs. Both methods should be utilized in establishing an initial dependable diagnosis of histoplasmosis at post mortem. *H. capsulatum* was demonstrated histologically intracellularly in proliferated histiocytes in most organs of the body with the exception of the brain and adrenals. The yeast form was recognized with the hematoxylin-eosin stain and identified with the Gomori's methenamine-silver stain and PAS reaction. In the kidneys the *Histoplasma* was found in the glomerular capillaries. It is well to mention that in the disseminated form the microorganism can be demonstrated in the urine and the method can be utilized in the clinical diagnosis of the disease. In systemic cases *H. capsulatum* may also be demonstrated in smears of bone marrow or cultivated. Mycological studies revealed the mycelial form of the fungus cultured in Saboraud agar and Mycosel incubated at room temperature. The natural mycelial form of the fungus was converted into the yeast form in subcultures in brain heart infusion agar slants enriched with defibrinated horse blood incubated at 37°C. This mycological processes revealed the diphasic nature of the fungus. The histoplasmin agglutinating test with the patient serum obtained before death was positive in a titer 1:32 dilution.

Histoplasmosis is a mycosis of the reticuloendothelial system with the intracellular growth in histiocytes or macrophages and proliferation of these cells. The disease is generally acquired by inhalation of *H. capsulatum* and the fungus is capable of producing disease in the acute and evanescent lesions with the formation of calcified nodules and chronic pulmonary forms with

cavitation simulating tuberculosis. When the *H. capsulatum* gains access into normal adults the disease is localized and usually becomes arrested in the form of chronic calcified nodules. However, in about 1% of infections it is manifested in a disseminated form. Disseminated infections are seen most often in children and debilitated adults suffering from some chronic disease like carcinoma, blood dyscrasis, lymphomas, diabetes and cirrhosis of the liver.

Summary

A case of disseminated histoplasmosis in a debilitated elderly adult suffering from granulocytic leukemia is presented. The pathology of the disseminated disease and mycological studies of the biphasic manifestations of the fungus have been discussed. The opportunistic nature of the fungus is rhetorically apparent in the discussion. This is the second reported case of systemic histoplasmosis in Puerto Rico to the best of our knowledge.

Resumen

Se presenta un caso de histoplasmosis sistémica en un adulto débil de avanzada edad con padecimiento de una leucemia mielocítica. Se discute la anatomopatología de la enfermedad diseminada y los exámenes micológicos de las manifestaciones bifórmicas del hongo. A nuestro mejor entender este es el segundo caso de histoplasmosis sistémica informado en Puerto Rico.

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CASE REPORT

REGIONAL ILEITIS

Laszlo Ehrlich, M. D., F. A. C. P.
Juan R. Monserrate, M. D.

Regional ileitis, though it is a rather common disease in the United States, is rare among Puerto Ricans. Since the report by Asencio (1) in 1946, to our knowledge, there has been no other published case involving a native Puerto Rican. It is the purpose of this report to present the clinical manifestations of this disease in a young veteran recently hospitalized at the San Juan Veterans Administration Hospital.

Case Report

A 35 year old white male was admitted because of crampy abdominal pain 5 to 6 hours after ingestion of food, gaseous sensation and flatucence in the abdomen and weight loss. The patient stated that ever since 1955 he had been having crampy abdominal pain mainly localized at the right lower quadrant associated with diarrhea and general malaise. Abdominal distention and peristaltic movements were also noted. Bowel movements were six to seven per day, yellowish in color and had a greasy appearance. He was hospitalized at another institution and told to have sprue. In 1958 he moved to New York. In 1960 he was hospitalized at the Manhattan Veterans Administration Hospital with the same symptoms. Except for a barely palpable liver, the physical examination was within normal limits. Pertinent laboratory data revealed a hemoglobin of 10 g/100 ml, 24 hr. fecal fat of 3.3 gms, normal glucose tolerance curve and guaiac positive stools. Small bowel series revealed a lesion in the terminal ileum. PPD was negative. The patient was started on steroids and approximately one month later symptoms of migratory polyarthritis of the knees and ankless appeared which required an increase in steroid dosage. A diagnosis of regional ileitis was then made. He improved and did fairly well with minimal abdominal complaints and was discharged.

In 1963 a small bowel study done at the New York Veterans Administration Regional Office showed a narrowed ragged terminal ileum with loss of normal mucosal markings. On January 1966, back in Puerto Rico, he entered another hospital with an exacerbation of his previous symptoms. He was treated for malnutrition unsuccessfully for 18 days. In June 1966 he was admitted to this hospital.

Physical examination revealed a cachetic pale male. Blood pressure was 90/60 mm Hg; pulse, 80/min.; temperature, 98°F. The mucosae were pale, the tongue normally papillated. The abdomen was soft but with generalized deep tenderness more marked on the right lower quadrant. No masses and on organs were palpable.

The hemoglobin was 10.7 g/100 ml: leukocytes, 5,800 per cu. mm.; showing 7% eosinophiles. Urinalysis, stools for occult blood, blood urea nitrogen, electrolytes, I-131 radioiodide uptake, tri-iodothybilirubin, alkaline phosphatase, serum turbidity, triolein absorption, cephalin flocculation, serum ronine, RBS uptake, calcium, phosphorus, serum glutamic oxalacetic transaminase, serum glutamic oxalacetic transaminase, serum glutamic pyruvic transaminase, lactic dehydrogenase, serum albumin and globulin and latex fixation were all normal. Cholesterol was 98 mg % and prothrombin time 15 secs. with a control of 11.8 secs.

From the Radiology and medical Services, Veterans Administration Hospital, San Juan, Puerto Rico.

Chest X-ray was negative. Small bowel studies showed abnormal distal ileal loops and there was evidence of an ileo-colic fistula. Barium enema also showed the ileo-sigmoid fistula and suggestion of another fistula in the same region. These findings were considered to be consistent with the clinical diagnosis of regional enteritis. Intravenous pyelogram was negative.

Jejunal biopsy showed an essentially normal jejunal mucosa.

Laparotomy was performed on June 29, 1966. An inflammatory mass was found in the right lower quadrant involving the distal ileum, lower sigmoid, cecum and right transverse colon. Upon dissection multiple fistulous communications were found between these structures. The appendix was not involved. The segments of bowel involved in the mass were greatly thickened and indurated as if forming the walls of a previous long-standing abcess. The mesentery of the distal ileum was also thickened. Right hemicolectomy with distal ileostomy and ileotransversostomy and closure of sigmoid fistula were performed.

Histologic examination of the ileum showed submucosal fibrosis and infiltration with inflammatory cells. Many of the lymphatics were dilated. Several granulomatous lesions with giant cells were identified, some of them in the muscularis. The ulcerated lesions of the distal ileum showed an intense chronic inflammatory reaction and fibrosis at the base of the ulcers. The mesentery showed fibrosis and perivascular infiltration with inflammatory cells and foci of granulomatous inflammation. The lymph nodes showed chronic lymphadenitis but no granulomas were evident. The appendix showed acute and chronic inflammation of the wall but his appeared to be a process originating outside the appendix rather than as a result of primary appendicitis.

Discussion

Regional ileitis is a disease of unknown etiology. It usually begins in the young age group, the peak incidence being between the ages of fifteen and thirty five, but it occurs also in older people. No specific cause of this disease has been identified. Bacterial and even viral etiologic agents have been suggested. Since the mesentery and the lymph nodes always participate in the lesion, it is felt by many that the primary change originates from the inflammation of the lymph nodes. Chess et al (2) were able to produce similar changes in the terminal ileum when dogs were fed with fine sand and talcum. However, at the present time it is felt that the enlarged and engorged lymph nodes of the mesentery seem to result from the submucosal inflammation rather than to be its cause.

Macroscopically the remarkable thickening of the wall of the ileum is characteristic. Frequently, the terminal portion is involved as was originally described by Crohn in 1932 (3), but other portions of the small bowel and the proximal colon may show similar changes. Skip areas of normal bowel are characteristic, but the most frequent single lesion is the terminal ileum.

The mesentery of the involved portion of the small bowel is hugely thickened and contains enlarged lymph nodes. Matting of various loops due to abcess formation or fistulae can be found. The mucosa of the involved segment shows ulcerations, superficial or deep, usually on the mesenteric side. Attempt of healing of these areas will cause strictures. The major microscopic changes were described by Otani (4). The earliest change is the submucosal thickening. Giant cells without caseation are present. Eventually, the primary granulomatous nodules are overshadowed by acute and chronic inflammation. Later, the entire process is obscured by submucosal and serosal fibrosis and scarring. In summary, the pathologic appearance of the lesion is quite variable.

The clinical picture of regional ileitis is also variable. It usually begins insidiously

with vague abdominal complaints, but it may have an acute onset, similar to an appendicitis. Later on, the abdominal pain increases, with some relief following defecation. In most cases, diarrhea is present. Occult bleeding causing iron deficiency anemia is frequent. Occasionally rheumatoid complaints (in about 5% of the cases) have been reported. When the process is extensive, symptoms and signs of malabsorption appear. Pimparker (5) found that involvement of less than 3 feet of the terminal ileum with an intact ileocecal valve does not cause steatorrhea. A slight anemia and minimal deficit in prothombin were the only evidences of malabsorption in the patients with only terminal ileal disease. According to Bockus (6), regional ileitis is one of the most frequent causes of secondary malabsorption among the patients admitted to the Graduate Hospital in Philadelphia. In Badenock's (7) series, it was the second most frequent cause of steatorrhea out of 163 cases. Weight loss is usual in active cases. The most important complication is the formation of fistulae without actual perforation into the free peritoneal cavity. The internal fistulae between small bowel segments short circuit the passage of intestinal contents, hamper absorption and intensify the diarrhea. At this stage the palpation is usually painful, mostly in the right lower quadrant of the abdomen. Remissions for several years occur, followed by unexplainable exacerbation of symptoms. The clinical picture does not seem to correspond to the anatomical situation. The variability of the pathologic changes and of symptoms must be kept in mind in order to understand the clinical picture of regional ileitis.

According to Marshak (8) who reported 750 cases of regional ileitis in 1955, the early X-ray changes consist of blunting and thickening of the valvulae conniventes. This appearance is not characteristic of any particular lesion. Later on ulcerations occur which produce longitudinal streaks, which are somewhat more characteristic. When cicatrization takes place, one may see a rigid, cast-like tube presenting no mucosal pattern. Skip areas are another characteristic feature. The transition of diseased to normal intestine is fairly abrupt. The next stage is the "stenotic phase". The stenosis may involve 1 or 2 cm or longer segments. The "string sign", considered as the pathognomonic manifestation of regional ileitis is usually observed in the distal ileum. Fistula formation and separation of the loops of the bowel due to thickening of the mesentery are also more frequent in the distal ileal region. The combination of regional ileitis and right sided ulcerative colitis was seen only 20 times in Marshak's series. He also points out that recurrent ileitis following side-tracking procedures with and without resection of the diseased bowel occurs frequently. Recurrences appear particularly in patients with fistulae.

In 1946 Asencio (1) reported 15 cases of "acute ulcerative ileitis". Upon review of the article we find that 9 out of 15 cases described were actually called regional enteritis or ileitis, acute or chronic; out of these 9, probably only four should have been called regional ileitis since the rest were either acute mesenteric lymphadenitis or were associated with a tuberculous process or overwhelming parasitosis. In one the pathological report was not included. No additional case has been reported from Puerto Rico since.

Review of the filed pathological reports at this hospital reveals three other cases of

regional ileitis. Two of them were in 1949 and 1950, respectively. Their clinical records are not available. The other case is a specimen sent from Susoni Hospital, Arecibo, Puerto Rico, for confirmation of the diagnosis. This record is not available either.

The present case has several interesting features. First of all it was diagnosed as regional ileitis in the United States where the disease is not uncommon (6). There has been no evidence of malabsorption probably because only the terminal ileum was involved (5). Undoubtedly the disease had started more than 10 years ago and, after a 6 year remission, became active with a clinical picture that lead to operation. The roentgen changes, demonstrating an abnormal ileal loop with fistulae (7, 9), the confirmatory findings at the operation and finally, the pathologic examination of the removed organs (3, 4), leave no doubt that our patient can be accepted as an authenticated case of regional ileitis.

Summary

A case of regional ileitis in a Puerto Rican veteran is presented. The clinical history, the roentgenological and histopathological findings are described. The scarcity of reports of this condition among Puerto Ricans, the absence of malabsorption, the associated arthritic components and eventually its complication by ileo-colic fistulae, are among the salient features of this case. This is one of the few fully documented cases of regional ileitis in a Puerto Rican.

Resumen

Se presenta un caso de ileitis regional en un veterano puertorriqueño describiéndose un cuadro clínico y hallazgos roentgenológicos e histopatológicos. El caso es de interés por la rareza de esta condición entre los puertorriqueños, la ausencia de malabsorción, el componente artrítico asociado, y las fístulas ileales-complicantes. Es este uno de los pocos casos bien documentados de ileitis regional en puertorriqueños.

Acknowledgement

Dr. J. H. Amadeo and his staff carried out the surgical procedure. Dr. G. A. Ramírez de Arellano studied the pathological material. We are indebted to both for their cooperation.

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Fig. 1: Small bowel study. The 2 hr. film shows aa rigid ileal segment in the right lower quadrant with destroyed mucosal pattern (arrow). A colonic loop is present projected over the lumbosacral level in the mid-abdomen (double arrow), representing a fistulous communication between it and the involved ileum.



Fig. 2: Similar findings, showing the colonic loop to better advantage.

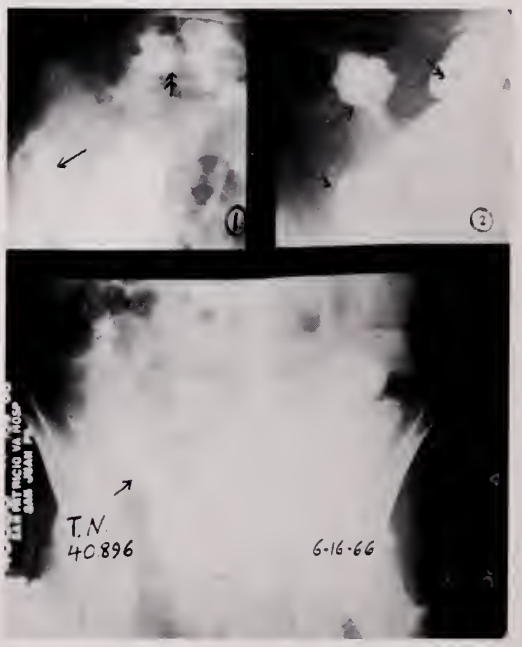


Fig. 3: Barium enema. The inserted spot films (in the upper half of the picture) taken at the early phase of fluoroscopy show the sudden appearance of an ileal loop (arrow) shortly after filling the recto-sigmoil (double arrow). The lower half of the film, taken after evacuation, again shows the abnormal ileal loop in the right lower quadrant. The examination therefore confirms the ileo-colic fistula, suggesting also the presence of another fistula in the same region. (Inserted spot film major portion (right side) is normal. The distal marked 2).

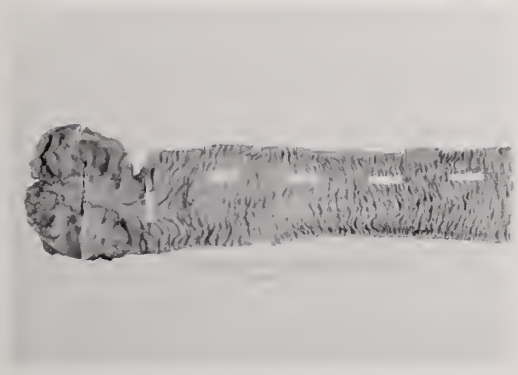
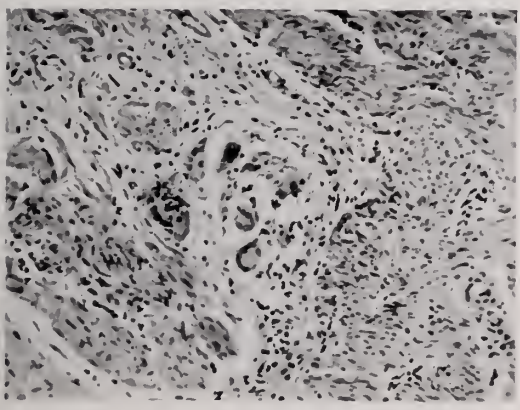


Fig. 4: Shows the resected ileal segment. The major partion (right side) is normal. The distal portion (left side), about 10 cm long, is abnormal, showing swollen mucosal folds and 2 long ulcerations.



Fig. 5: Close-up view of the involved distal ileum, showing the pathological changes to better advantage.



Gig. 6: Granuloma in the submucosa (100x).

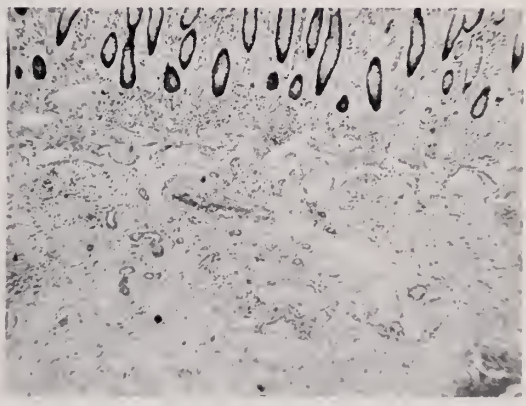


Fig. 7: Dilated lymphatics in the submucosa (35x).

CASE REPORT

MULTICENTRIC OSTEOGENIC SARCOMA

Jorge Bonilla-Colón, M.D., F.A.C.S.

Osteogenic sarcomas are malignant connective tissue growths which form neoplastic osteoid and osseous tissue in the course of their evolution. They are usually solitary, arise at either end of the shaft of a long bone, and do not tend to metastazise to distant parts of the skeleton.

The occasional case of osteogenic sarcoma with multiple skeletal involvement is of clinical significance. The present report deals with such a case and is added to the few scattered cases so far reported in the literature.

Case Report

A 12 years old boy was seen by us on consultation on August 4, 1962 with a history of pain in his right knee of about three months duration. Three weeks prior to examination swelling and local heat were noted and the pain became worse. He denied trauma or other symptomatology except the loss of appetite.

Examination revealed a pale boy of stated age in moderate distress due to pain in his knee. There was a warm, tender, firm swelling at the upper end of the right leg. Knee motion was restricted and painful. There was no evidence of knee effusion or of regional lymphadenopathy. The chest was clear to auscultation.

From the Crippled Children Service, Ponce District Hospital.

Read at the annual meeting of the Southern District Medical Society, Ponce, P. R., December, 1964.

X-Rays of the right knee (Fig. 1) revealed a sclerotic lesion of the upper end of the tibia with evidence of bone formation and bone destruction. The lesion was seen to invade the soft tissues and there was evidence of periosteal reaction manifested by a sunray appearance of the bone. These findings were considered diagnostic of osteogenic sarcoma. A chest X-Ray was negative.



Fig. 1: X-Rays of the right knee revealing a bone-forming lesion at the upper tibial metaphysis with extension to the adjacent soft tissues and periosteal reaction. A peculiar increase in bone density is also evident at the juxta-epiphyseal area of the femoral metaphysis, without bone destruction or reactive bone formation.

Biopsy was recommended. The child was taken to the Isaac González Martínez Oncologic Hospital and on September 5, 1962 after a frozen section biopsy the leg was amputated through the middle third of the thigh. The pathological report of the specimens was osteoblastic osteogenic sarcoma of the right tibia (Fig. 2).



Fig. 2: Histopathology of the lesion characterized by malignant connective tissue with neoplastic osteoid and bone formation.

There was an uneventful healing of the stump and the patient did fairly well for several weeks. On November 13, 1962 thirteen weeks after the original examination and nine weeks after amputation, the patient came again to us for examination because of pain and gradual swelling in his left knee. The physical findings were essentially similar to the ones presented in his right knee in the original examination but the swelling was more pronounced.

A radiographic survey of the skeleton revealed sclerotic foci involving mainly the metaphyseal regions of both femora, upper left tibia, and entire pelvis where there was evidence of a tumor mass in the right ischio-public region. There was involvement also of the lumbar vertebrae with collapse of the body of L_3. The inner end of the clavicles and upper metaphyses of both humeri were also involved (Figs. 3, 4, 5). A diagnosis of primary multicentric osteogenic sarcoma was made.

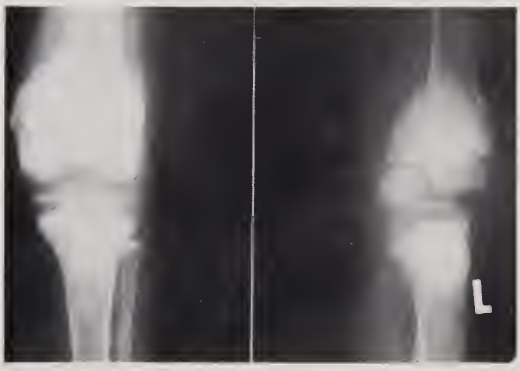


Fig. 3 X-Rays of the lef knee demonstrating the osteogenic sarcomatous involvement of the lower end of the femur and upper end of the tibia mainly at the metaphyseal areas. The tumor has already invaded the soft tissues adjacent to the femur.



Fig. 4: X-Ray of the pelvis with amputated right femur showing sclerotic lesions at the upper ends of both femora and both sides of the pelvis. A tumor mass is seen projecting from the right ischiopublic region into the pelvis.



Fig. 5: A chest film in which osteoblastic involvement of the medial ends of both clavicles and upper ends of humeri can be observed.

Cobalt therapy was given at the I. González Martínez Oncologic Hospital to a tumor dose of 1960 R in a period of thirteen days.

On December 12, 1962 the patient was admitted to Ponce District Hospital because of urinary retention of five days duration. Physical findings were essentially unchanged from previous examination except for increase in size of the lesions in his left knee.

The hemoglobin was 9.3 gm per 100 ml; the white cell count was 6,300 and the erythrocytes 3,200,000 per cu. mm. The urine was normal except for the finding of 15-20 leukocytes per HPF and many bacteria in the sediment. The urea nitrogen was 6 mg. calcium, 14.5 mg per 100 ml. The alkaline phosphatase was 14 KA units.

A cystoscopy revealed elevation of the floor of the bladder suggestive of extrinsic pressure. Indwelling Foley catheter drainage was recommended by the urologist.

The patient rapidly developed symptoms of cord and nerve root pressure manifested by paralysis and anesthesia of the left lower extremity. His condition continued deteriorating at a fast pace and he expired on January 13, 1963, a month after admission to the hospital and approximately eight and a half months after the onset of his complaints. The autopsy permission was denied.

Discussion

Jaffe (2) includes in the group of primary multicentric osteogenic sarcomas those in which foci of osteogenic sarcoma develop in multiple bones more or less simultaneously and apparently *de novo*.

It is not unusual to see multicentric foci of osteogenic sarcoma in bones affected by Paget's disease but these are generally excluded from the group of primary multicentric osteogenic sarcomas. The occasional rare case of osteogenic sarcoma with one or more skeletal metastases is also excluded from the group.

Among the few scattered cases of multiple osteogenic sarcomas occurring simultaneously in numerous bones of the skeleton the one by Busso and Schajowicz (1) from Argentina is perhaps one of the first reported and most representative. An eight years old girl presented multiple sclerotic tumor foci in many of the bones predominating in areas of most active bone growth. Moseley and Bass (5) observed another girl, five years old, with practically identical radiographic features, i.e., multiple areas of dense new bone formation through-out the skeletal system.

Another case of osteogenic sarcoma with multiple skeletal as well as visceral deposits considered to be of multicentric origin is that reported by Halpert et al (3) of a girl

seven years old with the initial tumor in her right knee followed a month later by tumor in her left ankle. About four months after onset the X-Rays showed opacities in both lungs and multiple tumors in the dorsal and lumbar vertebrae, pelvis, femora, tibiae, tarsal bones, one humerus, right ulna and radius and two metatarsal bones.

The patient died four and a half months after the first signs of the disease and at autopsy osteogenic sarcomas were identified in the lungs, heart, ovaries, vertebrae and pelvis.

Lichtenstein (4) published the roentgenograms of a 15 years old boy, which he regarded as probably representing multicentric osteogenic sarcomas; however, no pathological studies were done in his case. He concludes that "altogether, it would appear that osteogenic sarcoma developing in multicentric foci is not as rare as one might imagine, although relatively little has been published on the subject".

In the case reported by Busso and Schajowicz (1) there was no roentgen evidence of pulmonary involvement. The cases reported by Halpert et al (3) and by Lichtenstein (4) however, showed numerous metastases in the lungs. The course of the disease in all the cases mentioned as well as in the present case was extremely rapid.

Price and Truscott (6) reported their experience of a case of primary multicentric osteogenic sarcoma in an adult not affected by Paget's disease. In their case too, the lungs were found free of metastases.

In none of the instances cited had there been any exposure to beryllium, radium or other radioactive substances which may stimulate the production of bone sarcoma.

Summary

A twelve years old boy with multiple bone sarcomas appearing almost simultaneously at several sites of the skeleton is reported. A pathological study of the resected specimen demonstrated osteogenic sarcoma of an osteoblastic type. We believe that this rare case fulfills the criteria of the so-called primary multicentric osteogenic sarcomas because of its similarity to several other cases already reported in the literature.

Resumen

Se informa el caso de un varón de 12 años de edad con sarcomas múltiples de hueso que se manifestaron casi simultáneamente. El estudio histológico demostró sarcoma osteogénico del tipo osteoblástico. Los autores consideran que este caso puede clasificarse como uno de sarcoma osteogénico multicéntrico primario.

Acknowledgements

We acknowledge the help of Dr. Raúl Marcial-Rojas, Head of the Department of Pathology at the Isaac González Martínez Oncologic Hospital and U.P.R. School of Medicine, who kindly allowed us to use the pathologic material in Fig. 3, and Mr. Antonio Puras, of the same institutions, who did the excellent photographic work.

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EDITORIAL

TOM DOUGLAS SPIES: A TRIBUTE FROM PUERTO RICO*

It was in December 1945 when Tom Spies bringing with him some synthetic folic acid walked into one of the wards of the now extinct University Hospital of the School of Tropical Medicine of Puerto Rico when we were making rounds and Ramón Suárez Jr. was doing a sternal marrow aspiration on a severe case of sprue. It was white woman 30 years of age weighing 58 pounds. She was the first patient ever to receive folic acid in Puerto Rico.

This woman whose picture you have probably seen in papers published in 1947 (1) served many years later for Butterworth, Crosby and Enrique Pérez' studies of jejunal biopsies in tropical sprue. She is still living and working actively 21 years later thanks to folic acid and to Tom Spies.

Before the advent of synthetic folic acid, we had obtained good results in the treatment of sprue with parenteral administration of liver extract. We had learned from Bill Castle who had visited Puerto Rico in 1931, how to prepare the injectable crude liver extract using the powdered preparation known as Colin's fraction or Lilly's 343.

At the time of Tom Spies first visit to Puerto Rico we were actively studying the effect of various liver fractions supplied to us by the late Dr. Subba Row of Lederle Laboratories at Pearl River in New York. Nothing was then known of folic acid and of vitamin B_{12}.

From 1947 to 1948 we tested folic acid conjugates known as Bc obtained from yeast by Pfiffner and collaborators of Parke-Davis & Co. and shortly afterwards we were trying Diopterin, Triopterin, Formyl-folic acid and Citrovorum factor, all of them generously supplied by J. M. Jukes of Lederle Laboratories.

It might be of interest to recall that one of our typical sprue patients developed a fulminant attack of combined system disease becoming paraplegic

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* *Read at University of Alabama Medical Center in Birmingham, Ala. on March 24, 1966.*

while in perfect hematologic remission under Diopterin therapy. This patient's gastric juice not only contained free hydrochloric acid, but after incubation with beef it induced a reticulocytic response when administered to a known case of Addisonian pernicious anemia.

About 3 years after the introduction of synthetic folic acid and while studying the effect of its various derivatives we were suddenly and agreeably surprised by the visit of Miss Jean Grant, able and loyal collaborator of Tom Spies, bringing with her a few micrograms of the newly discovered vitamin B_{12}.

The effectiveness of vitamin B_{12} *in 5 cases of sprue was reported in 1948 (2). We had obtained maximal reticulocytic response with a single intramuscular dose of as little as 100 micrograms. Vitamin* B_{12} *proved to be the most potent antianemic substance known to science.*

Shortly afterwards we studied the comparative effect of vitamin B_{12} *administered orally, sublingually and intramedullary into the iliac crest to arrive at the conclusion, well known to all of you, that the intramuscular is the easiest, safest and most practical route of administration.*

The marked decrease in mortality from sprue and other anemias during the last two or three decades is evident in Tables I and II.

TABLE I: DEATHS FROM SPRUE (3)

Year	*Number*	*Rate*
1933	161	9.8
1950	32	1.4
1964	16	0.6

TABLE II: DEATHS FROM ANEMIA (3)

Year	*Number*	*Rate*
1941	421	22
1945	322	15.7
1950	197	8.9
1964	132	5.1

It may be pertinent to leave aside historical events and say a few words about Tom Spies.

The following paragraph transcribed from an Editorial in the Journal of the Southern Medical Association when Tom Spies was named President-Elect in 1959 describes Tom exactly as I knew him:

"With a life fully dedicated to the cause of medicine, Dr. Spies has had neither the time nor the desire to surround himself with the comforts and conveniences regarded by most people as important aspects of living. On the contrary, he lives frugally and simply, apparently little concerned about his personal financial gain. He has never accepted a professional fee from an individual patient. Furthermore, he has never accepted one penny of public funds for the construction and operation of his extensive facilities."

As a person he was a warn and generous friend. Jenner would have described him by stating that he had "the generosity of a good man and the simplicity of a great one." He was sincere, unassuming and witty. He had wisdom and courage, buoyant optimism, subtle humor, warn understanding and a great love for the human being in sickness, pain, disability and distress.

As a doctor he was the "compleat physician" of the Britishers, specialized in "Human Being." He had compassion, warmth, kindness and charity. He had the ability to talk intelligently and listen sympathetically to patients rich or poor, young or old, white, black or yellow, Christian or agnostic. To the patient he was a keen clinician and a good Samaritan.

As a researcher he had a fertile mind, wisdom and creativeness and a constant and indefatigable willingness to work. He had the skill to tie together science and practice, the ability to build without destroying, the gift to inspire and help, never to limit or restrict the work of others. And above all, he was an honest investigator who had learned "to see what he looks at, and not what he looks for."

Tom Douglas Spies was a prominent citizen of the state of Texas and of course a most distinguished American citizen. By the power of his genius and the wealth of his achievements which were universally acknowledged, he became a citizen of the world and by his unselfishness, modesty, generosity and charity he is now, I hope and believe, a citizen of Heaven.

Ramón M. Suárez, M. D.

References

1. *Suárez, R. M., Spies T. D., Suárez, Jr. R. M.*: The use of folic acid in sprue. Ann. of Intern. Med. 26: 643, 1947.
2. *Spies, T. D., and Suárez, R. M.*: Response of tropical sprue to vitamin B_{12}. Blood, 3; 1213, 1948.
3. Data Supplied by Mrs. González of the Division of Vital Statistics of the Department of Health of Puerto Rico.

RESUMENES

ABSORCION DE HIERRO EN LA HEPATITIS AGUDA. (Iron Absorption in Acute Hepatitis) L. A. Turnberg, M. D. Amer. of Dig. Dis. 2:No. 1, 20-26, Jan., 1966.

Fueron estudiados cinco pacientes con hepatitis infecciosa, seis con cirrosis, cuatro con ictericia obstructiva y seis normales. La prueba de absorción férrica se practicó utilizando Fe radioactivo administrándolo por boca. Se determinó la concentración del Fe radioactivo en excreta durante siete días. Además de ello, se hicieron determinaciones de Fe serico y la capacidad de ligar hierro en sangre (IBC).

La capacidad para ligarse al Fe estaba reducida en el grupo con hepatitis al igual que en los cirróticos; era normal en los casos con ictercia extrahepática. El hierro serico estaba aumentado en los casos con hepatitis y cirrosis. El porcentaje de saturación de la siderofilina estaba igualmente aumentado en los casos de hepatitis, al igual que en los cirróticos.

La absorción de Fe se encontró aumentada en los casos de hepatitis y cirrosis pero normal en los casos de ictericia extrahepática.

Los autores postulan que el aumento en la absorción de Fe en casos de hepatitis y cirrosis se origina por deficiencia pancreática, pues es conocido que experimentalmente el extracto exocrino de páncreas produce disminución en la absorción de Fe. La deficiencia pancreática se explicaría por la alta incidencia de pancreatitis crónica en pacientes con cirrosis.

Miguel A. Sarriera, M. D.

ENFERMEDAD CRONICA CARDIACA DEBIDO A OBESIDAD (Chronic Heart Disease Due to Obesity) James K. Alexander, M.D. J. of Chronic Dis. 18: 895-898, Sept., 1965.

Este estudio se hará en observaciones hechas en 50 casos de pacientes con obesidad extrema con miras a hacer un recuento de los hallazgos circulotarios en la obesidad y tratar de desarrollar la entidad enfermedad cardiaca debido a obesidad.

Estos pacientes fueron observados por espacio de 2 a 5 años. El peso iba de 250 a 500 libras; siendo el promedio 300 libras.

Describe el autor las siguientes observaciones: Usando una aguja intra-arterial y un electromanometro se medió la presión arterial de forma directa encontrándose que 60% de estos sujetos eran hipertensos en un grado moderado. La hipertensión es común en estos pacientes pero como 40% eran normotensos hace pensar que la obesidad no necesariamente va acompañada de desarrollo de hipertensión. No se encontró correlación entre niveles de elevación de presion y grado de obesidad indicados por la cantidad de peso en exceso. Se comparó el método directo al método clínico usual con un brazal; pensando que el aumento de diámetro del brazo en los obesos iba a interferir con la lectura; pero se encontró que en la mitad de los casos ambas lecturas eran iguales y que sólo 25% de los pacientes tenía niveles más altos con el método usual de brazal. La causa de esta elevación de presión no se comprende fácilmente ya que la resistencia vascular sistémica es normal; no pudiendo de esta manera implicar que exista vasoconstricción arteriolar. Aboga este autor por usar un regimen de reducción de peso y dieta baja en sodio para el manejo de esta hipertensión y dejar las drogas antihipertensivas para pacientes que no se controlan con este regimen.

En 40 obesos encontró el autor que existe un aumento en el volumen total sanguíneo; medido con la técnica del azul de Evans; este aumento en el volumen sanguíneo tiene una correlación estadística con la cantidad de exceso de peso. También se encontró un aumento en débito cardíaco.

Se hizo estudios del diámetro transverso del corazón en pacientes hipertensos y normotensos mediante radiografías y aunque este método tiene sus limitaciones se encontró un aumento en el diámetro del corazón relacionado con aumento de peso en 100% de los casos. Para delucidar el porqué de esta cardiomegalia se hicieron estudios postmorten en obesos que murieron de forma accidental o infecciones fulminantes. No se encontró en la autopsia evidencia de enfermedad coronaria, reumática u otra enfermedad cardíaca reconocida pero sí una relación entre el aumento del tamaño del corazón con exceso de peso.

El mecanismo de la hipertrofia del miocardio en los obesos no está claro. Se cree que está relacionada parcialmente con un aumento en el trabajo del corazón. En estos pacientes el traba-

jo del corazón es mayor ya que débito cardíaco puede aumentar en reposo y máxime si hay hipertensión arterial donde la sobrecarga del corazón es mayor. Este aumento del trabajo cardiaco, de volumen y presión está parcialmente relacionado al desarrollo de la hipertrofia del miocardio y de la insuficiencia cardíaca que se ve clinicamente.

Esta insuficiencia ocurrió en 10% de los pacientes vistos en este estudio con o sin elevación de la presión arterial. Es difícil llegar a su diagnóstico clínico; la presión venosa central no está elevada y debido a la obesidad no vemos regurgitación de las venas del cuello. Aquí está justificado dar tratamiento de prueba y ver la respuesta clínica del paciente.

Se ve que al reducir de peso la presión arterial; volumen sanguíneo, y el débito cardíaco disminuyeron. También disminuye el tamaño del corazón y lo que no se sabe si ocurre, es la regresión de hipertrofia miocárdica; aunque en animales si que se ha observado.

La obesidad representa un estado de débito cardíaco elevado y puede en último caso producir insuficiencia cardíaca congestiva y cuando ocurre es una condición tratable.

Francisco X. Veray, M. D.

PATOLOGIA CARDIACA EN EL CORAZON DEL OBESO EXOGENO CRONICO (The Cardiac Pathology of Chronic Exogenous Obesity) Kamel H. Amad, M. D., J. C. Brennan, M.D., and James K. Alexander, M.D. Circulation 32:740-745, Nov. 1965.

Se examinaron los resultados macro y microscópicos cardíacos en la necropsia de 12 sujetos con obesidad marcada (6 hombres, 6 mujeres). En cada caso se pudo ver que el peso del corazón era considerablemente mayor que el predicho en condiciones de peso ideal. Nueve de los doce sujetos se le encontró marcada hipertrofia de la pared ventricular izquierda y dos hipertrofia derecha. El aumento de peso cardíaco y de espesor de la pared ventricular se debió a hipertrofia muscular ya sea del ventrículo izquierdo o de ambos ventrículos (izquierdo y derecho). No se encontró en ingún caso hipertrofia ventricular derecha aislada o predominante. Estos hallazgos están en armonía con la evidencia clínica y física que la obesidad exógena crónica no lleva a cor pulmonale aislado en la ausencia de émbolos pulmonares.

Se vió en este estudio que la hipertrofia del miocardio es una alteración anatómica más específica y significativa de los corazones de los obesos; que las que anteriormente se habían preconizado; tales como acumulación excesiva de grasa en el epicardio o infiltración de grasa miocárdica.

Aunque los estudios no dieron luz sobre el posible mecanismo de esta hipertrofia cardíaca; se ha visto que hay un aumento del trabajo cardíaco en las personas obesas y es muy probable que este factor juegue un papel significativo. Un estudio reciente llevado a cabo por Alexander publicado en el American Journal of Cardiology en 1964 demuestra que el trabajo del corazón del obeso en descanso es mayor que aquel predicho para normotensos de peso ideal. Este cambio se produjo entero por aumento de trabajo del ventrículo izquierdo; que a su vez se relacionó con la cantidad de libras de sobrepeso.

Los hallazgos de este estudio han ayudado a sentar las propuestas alegaciones que en los obesos sin evidencia de enfermedad cardíaca ocurren manifestaciones de insuficiencia cardíaca predominando el fallo izquierdo o biventricular y que cor pulmonale aislado no ocurre a no ser que haya embolia pulmonar.

Francisco X. Veray, M.D.

LA HISTORIA NATURAL DE LA FIEBRE REUMATICA Y LA ENFERMEDAD REUMATICA CARDIACA—REPORTE A LOS 10 AÑOS DE UN ESTUDIO CLINICO COOPERATOIVO CON EL EMPLEO DE ACTH, CORTISONA Y ASPIRINA. *(The natural history of rheumatic fever and rheumatic heart disease the years report of a cooperative clinical. Trial of AGTH, cortisone, and aspirin)* Circulation, 32: Núm. 3 457-476, Sept. 1965.*

* *A joint report by the Rheumatic Fever working party of the Medical Research Council of Great Britain and the subcommittee of Principal Investigator of the American Council on Rheumatic Fever and Congenital Heart Disease, American Heart Association.*

Los hallazgos clínicos diez años después de finalizado el tratamiento en 497 niños, hasta la edad de 16 años, padeciendo de enfermedad reumática cardíaca, presentaron que el pronóstico no está influído por el uso de una droga sobre otra.

El estudio se llevó a cabo desde el 1951-1952; por investigadores de Estados Unidos de América, Canadá y Gran Bretaña; y tenía como propósito comparar los efectos de ACTH, cortisona y aspirina en la evolución futura de fiebre reumática. A los 10 años, 397 (79.9%) estaban vivos; 23 (4.6%) habían muerto, incluyendo 19 con fiebre reumática y enfermedad reumática cardíaca y 77 (15%) se había perdido contacto con ellos. No se vió enfermedad cardíaca residual en 94% de los casos que inicialmente padecieron carditis; en 70% de los casos que inicialmente tuvieron carditis sin enfermedad cardíaca reumática pero con un soplo sitólico apical grado I; en 74% de los casos con carditis inicial sin enfermedad reumática cardíaca pero con un soplo sistólico apical grado II o III; en 32% de los casos que inicialmente estuvieron en insuficiencia cardíaca congestiva o/y pericarditis; en 40% de los casos con enfermedad cardíaca preexistente inicialmente pero sin pericarditis o insuficiencia cardíaca y en 11% de los casos con enfermedad cardíaca preexistente con pericarditis o/e insuficiencia cardíaca.

Se diagnosticó estenosis mitral en 18 casos de 347 casos finalizados los 10 años y en 7 de 19 casos de muertes con fiebre reumática o enfermedad reumática cardíaca. Es más, su incidencia de estenosis mitral aumentó, con la severidad de la enfermedad al comienzo del tratamiento.

Recurrencias tratadas sin que hubiese enfermedad cardíaca preexistente obscurecían el pronóstico, pero no el aumento de incidencia de estenosis mitral.

El sexo femenino tuvo peor pronóstico que el masculino y fue más común la estenosis mitral en el sexo femenino.

Francisco X. Veray, M. D.

ESTUDIOS CROMOSOMICOS EN 156 PACIENTES CON ENFERMEDADES CONGENITAS DEL CORAZON. (*Chromosome studies in 156 patients with congenital heart disease*). *J. M. Anders, M. D., E. C. Moore, M. D. and H. Emanuel, M. D. Brit, Heart J. 27: Núm. 5, 756-762, Sep. 1965.*

No se encontraron anormalidades cromosómicas en una serie de 156 pacientes con enfermedades congénitas del corazón. (Familiar en 22 pacientes; defecto análogo en familiares en 18 ocasiones).

El número modal fue 46 en todos los casos aunque según se avanza en edad aumenta el número de células hipomodales. Se vió variación en el tamaño de ciertos cromosomas especialmente en el par número 16.

..En un paciente con coactación de la aorta se vió que las extremidades usualmente cortas del par 15; estaban marcadamente alargadas.

Francisco X. Veray, M. D.

SURGICAL TREATMENT OF ACQUIRED LESIONS OF THE AORTIC ORIFICE (*Le Traitement Chirurgical des Lesions Acquises de L'Orifice Aort¹que*) *Ch. Dubost Ph. Blondeau, A. Piwnica, Cl. d'Allaines, J. P. Cachera et D. Guilmet Archives Des Maladies Du Coeur et des Vaisseaux 58: No. 7, 1035-0143, 1965.*

On the basis of experience with 87 cases, the authors first give the elements that have combined together to make possible, in current practice, surgery of the acquired aortic valvular lesions: (1) The improvement of the techniques of extra corporeal circularion. (2) The introduction of prosthetic valves, specially the ball valve of Starr-Edward. They divided the indications in two headings: Calcific Disease: It is mainly stenosing, and in ⅓ of the cases approximately, it requires a decalcification which restores the flexibility of the cusps. In 2/3 of the cases, it indicates a valvular resection and its replacement by a prosthetic valve of the Starr type which they have 39 cases. Aortic Incompetence: Particularly when it results from bacterial endocarditis, which assumes a malignant form. The operative indication is sometimes a real emergency, and only the use of a prosthetic

valve which through the restoration of normal hemodynamic conditions, allows for a complete recovery.

However, one should be reserved in what concerns the future of the patients with a prosthetic ball valve, as secondary or delayed incidents have been observed. These authors among the many risk already published; in there series found: partial or total disinsertion of the prosthetic valve translated by the aparition of a diastolic murmur in 3 cases; and secondary bacterial endocarditis after the valve replacement in one case.

These risks had the authors to recommend the use of these prosthetic valves only in the cases in which the vital prognosis is involved within a short time.

Francisco X. Veray, M.D.

INCOMPLETE LEFT BUNDLE BRANCH BLOCK AND MYOCARDIAL INFARCTION. (*Bloc incomplet de la Branche Gauche et Infartus du Myocarde*) *J. Baragan, P. Maurice et J. Linigre. Archives de Maladies du Coeur et des Vaisseau* 58: *No.* 7, 909-921, 1965.

This clinical anatomical study of 68 cases with a pattern of left incomplete bundle branch block was preformed in order to look for eventual electrical signs, diagnostic of the association of myocardial infarction and patterns of left incomplete bundle branch block. It demonstrated that only the presence of a Q wave in leads 2 and 3 is sufficient to suggest the presence of posteroseptal infarction.

Among these 68 case, 41 "control" ones included cases of heart disease without myocardial infarction and 27 cases of myocardial infarction of various localizations. In this latter group, the anteroseptal areas was affected in 15 cases, the posteroseptal area in 22 and the lateral area in 4 cases.

After analysis of the various electrical signs under the double aspect of reliability and sensitivity, the diagnosis of association between myocardial infarction and left incomplete bundle branch block appeared to be more difficult and more hazardous than in cases of association with left complete bundle branch block.

The vectorial signs put forward by grant did not make it possible, in this anatomical series, to differentiate a left bundle branch block from a peri-infarction block.

Francisco X. Veray, M.D.

INJECTABLE AJMALINE IN THE TREATMENT OF PAROXYSMAL TACHYCARDIA: 40 *CASES.* (*"L" Ajmaline Injectable Dans Le Traitment Destachycardies Paroxystiques, a propos de* 40 *observations*) *P. Beriel, C. Boulard, F. Gal*[1]*nier, J. P. Boun House Etg. Cu Boucher. Archives des Maladies du Coeur et des Vaisseaux* 58: *No.* 7, 940-955, 1965.

The ajmaline is a Rauwolfia alkaloid (Kleinsorge, H. et all, Munch Med. WSCHR, 102, 2353, 1960). These authors have come to the conclusion that injectable ajmaline is the drug of choice in the treatment of paroxysmal tachycardia. This report is base on the experience with 40 cases (15 supraventricular tachycardia; 22 ventricular tachycardia and 3 atrial flutters). Administration can be either by slow injection of 50 mg intravenously at 1 cc/minute or by intravenous perfusion with 150-300 mg of isotonic glucose. In 10 cases, additional intramuscular injections were given every 6 hours. Alternating with the injections, ajmaline was given per os at 30-40 mg. per day. In the correction of ventricular tachycardia, this agent restored stable sinus rhythm immediately in 20 out of 22 cases. It is promising for use following myocardial infarction (prolonged or complete recovery in 7 out of 11 cases).

In cases of supraventricular tachycardia, it is also effective (13 out of 15 successes), but the high dosage sometimes required may increase the risk disproportionately if the attack is mild. Although it is well tolerated, patients most be monitored by ECG; any widening of the QRS calls for immediate cessation of treatment. The main objection to its use in paroxysmal tachycardia is the instability of its action, which might promote a recurrence. It is poorly tolerated in the aged (over 75 years).

Francisco X. Veray, M.D.

NOTICIAS

Locales

BOLETINES VIEJOS

La Asociación Médica de Puerto Rico está interesada en obtener copia de los siguientes números del Boletín:

Año	*Meses*
1921	enero a diciembre
1922	" " "
1923	" " "
1924	" " "
1925	" " "
1926	" " "
1927	" " "
1928	" " "
1942	" " "
1943	" " "
1944	" " "
1953	abril, junio y agosto.
1956	enero a diciembre.
1957	agosto.
1962	julio.

Aquellos miembros de nuestra matrícula que tengan estos volúmenes y deseen donárselos a la Asociación Médica, favor de comunicarse con el Sr. Eulogio Bermúdez Vélez, Secretario de Redacción.



SERVICIO DE BIBLOTECA

La Sra. Lillian Casas de López, bibliotecaria de la Escuela de Medicina, nos informa que las facilidades de esa dependencia están dispuestas para el uso de los médicos que residen en el área metropolitana. Los médicos de otros puntos de la isla pueden usar el servicio de fotocopias y las facilidades de la Biblioteca Nacional de Medicina.

Enumeramos a continuación las reglas más importantes que rigen los servicios de la biblioteca:

1. Todo médico que desee hacer uso de la biblioteca deberá completar una tarjeta de identificación.
2. Los libros se prestan por un mes, sin excepciones, y se pueden renovar una vez si no han sido reservados por otra persona. Ninguna persona puede tener más de siete libros fuera al mismo tiempo.
3. Las revistas encuadernadas se prestan por dos semanas, y se renuevan como los libros.
4. Las revistas sin encuadernar se prestan por un día solamente y no se renuevan.
5. Los últimos números de las revistas no circulan fuera de la biblioteca, excepto en caso verdaderamente necesario.
6. Los libros de referencia (incluyendo diccionarios, enciclopedias y otros libros generales) no circulan fuera.
7. El material listo y preparado para encuadernar no se prestará para fuera.
8. A nadie le está permitido sacar libros, revistas, u otro material sin dejar un recibo firmado por el mismo.
9. La persona que firma por un libro, revista u otro material, será responsable por él. Evite pasar a otra persona libros sacados por usted. Libros o revistas perdidos serán cobrados según su valor actual. Si éste no se puede determinar se cobrará $5.00. Libros rotos o mutilados se cobrarán también.
10. Se pueden obtener copias fotostáticas (Xerox) de artículos en libros o revistas a un costo de 20¢ la página.

Cualquier información adicional sobre este servicio se puede obtener de la señora Casas de López.

ECFMG EXAMINATIONS FOR 1966

Completed application must be received by ECFMG NOT LATER THAN November 15, 1966 for the Candidate to be admitted to the Examination to be given on February 15, 1967 and not later than June 13, 1967 for the candidate to be admitted to the Examination to be GIVEN ON September 13, 1967.

Council's new address:

3930 Chestnut St. Philadelphia, Pa. 19104, U.S.A.

Telephone: Area Code 215: 386-1300

Cable: Edcouncil, Philadelphia, Pennsylvania, U.S.A.

CONGRESO DE NEUROCIRUJANOS

Del 17 al 22 de octubre se reunirán en los salones del Hotel Americana el Congreso de Neurocirujanos. Los médicos locales están invitados a asistir al programa científico, cuyo tema es Infecciones del Sistema Nervioso. El programa es el siguiente:

Wednesday, October 19

Presiding Officer - John R. Russell

8:00 A. M. The Diagnosis and Antibiotic Treatment of Acute Bacterial Meningitis
Paul F. Wehrle, M. D.

8: 30 A. M. Fungal Infections of the Central Nervous System
John P. Utz, M. D.

9:00 A. M. Viral and Post-Viral Encephalomyelitis: A Survey with Neurosurgical Orientation
Leonard Berg, M. D.

9:30 A. M. Pharmacology and Modes of Action in Relation to Clinical Antimicrobial Therapy
J. P. Sanford, M. D.

10:00 A. M. Coffee Break
Presiding Officer - William H. Mosberg, Jr.

10:20 A. M. The Sequelae of Infections of the Nervous System
A. L. Sahs, M. D.

10:50 A. M. Pathology of Chronic Inflammation in the Nervous System
Sarah Luse, M. D.

11:20 A. M. Introduction of Residents in Training
Introduction of Honored Guest

11:30 A. M. Cerebral Venous and Sinus Thrombosis
Professor Dr. Hugo Krayenbuhl

12:00 - 1:00 P. M. Panel Discussion
A. L. Sahs

REUNIONES

Septiembre 4 — Día del Médico. Solicite información adicional a la Asociación Médica de Puerto Rico, teléfono 725-6969.

Septiembre 7 — Seminario en gastroenteritis, auspiciado por la Academia Americana de Práctica General y la firma Eli Lilly, S.A., en el anfiteatro de la Asociación Médica de Puerto Rico, comenzando a las 8:00 p.m.

Octubre 6-8 — Convención de la Sección de Siquiatría, Neurología y Neurocirugía, en el anfiteatro de la Asociación Médica de Puerto Rico.

Octubre 31 — Convención Anual de la Sociedad Americana de Medicina Tropical e Higiene, en el Hotel Americana.

Noviembre 15-19 — Asamblea Anual Asociación Médica de Puerto Rico, Hotel San Juan, San Juan, Puerto Rico.

Noviembre 21-25 — 8:00 p. m. — Conferencia por el Dr. Albert Montgomery Kligman auspiciada por el "American Academy of General Practice" y la Sección de Medicina General de la AMPR, en los salones de la Asociación Médica de Puerto Rico.

CONFERENCIAS AUSPICIADAS POR LA SECCION DE OBSTETRICIA Y GINECOLOGIA

La Sección de Obstetricia y Ginecología de la Asociación Médica de Puerto Rico auspiciará una serie de conferencias y películas para los médicos y el público, en el anfiteatro de la Asocia-

ción Médica de Puerto Rico. Estas conferencias y películas comenzarán a las 8:00 p.m. y se celebrarán en las siguientes fechas:

Octubre	Noviembre	Diciembre
6	3	1
13	10	8
20		15
27		

NACIONALES

AMERICAN COLLEGE OF PHYSICIANS POST GRADUATE COURSES

Sept. 28-*Oct.* 1 — Advances In Cutaneous Medicine Rochester, Minn.
Oct. 3-7 — The Care of the Critically ill Medical Patient, Syracuse. N. Y.
Nov. 7-11 — Endocrine And Metabolic Disorders, Brooklyn, N.Y.
Nov. 14-18—Newer Aspects of Experimental and Clinical Allergy, Boston, Mass.
Nov. 28-*Dec.* 2 — Progress in Gastroenterology-1966, Philadelphia, Pa.
Dec. 5-9 — What the Internist Should Know About Cancer, New York, N. Y.
Dec. 14-17 Infectious Diseases, Pittsburgs, Pa.

SYMPOSIUM ON INDUSTRIAL MEDICINE

October 20-22 — Symposium on Industrial Medicine: *The Doctor's Role in Occupational Health.* Mound Park Hospital Foundation, Department of Medical Education of the Mound Park Hospital, Bay Pines V. A. Hospital, Pinellas Country Medical Society, University of South Florida Division of Continuing Education, American Academy of General Practice. The Foundation reserves the right to limit registration. —Fee, $40. 18 Accreedited Hours by the American Academy of General Practice. Address Industrial Medicine, Mound Park Hospital Foundation, Inc., St. Petersburg, Florida 33701.

DECLARATION OF HELSINKI

(A code of ethics on human experimentation was adopted by the World Medical Association (WMA) at the World Medical Assembly, held in Helsinki in June 1964. This document known as the Declarations of Helsinki is the final expression of an earnest examination of the subject extending over several years.)

Recommendations Guiding Doctors in Clinical Research

Introduction. It is the mission of the doctor to safeguard the health of the people. His knowledge and conscience are dedicated to the fulfillment of this mission. The Declaration of Geneva of the World Medical Association binds the doctor with the words: "The health of my patient will be my first consideration" and the International Code of Medical Ethics declares that "Any act or advice which could weaken physical or mental resistance of a human being may be used only in his interest."

Because it is essential that the results of laboratory experiments be applied to human beings to further scientific knowledge and to help suffering humanity, the World Medical Association has prepared the following recommendations as a guide to each doctor in clinical research. It must be stressed that the standards as drafted are only a guide to physicians all over the world. Doctors are not relieved from criminal, civil and ethical responsibilities under de laws of their own countries.

In the field of clinical research a fundamental distinction must be recognized between clinical research in which the aim is essentially therapeutic for a patient, and the clinical research, the essential object of which is purely scientific and without therapeutic value to the person subjected to the research.

I. Basic Principles

1. Clinical research must conform to the moral and scientific principles that justify medical research and should be based on laboratory and animal experiments or other scientifically established facts.

2. Clinical research should be conducted only by scientifically qualified persons and under the supervision of a qualified medical man.

3. Clinical research cannot legitimately be carried out unless the importance of the objective is in proportion to the inherent risk to the subject.

4. Every clinical research project should be preceded by careful assessment of inherent risks in comparison to foreseable benefits to the subject or to others.

5. Special caution should be exercised by the doctor in performing clinical research in which the personality of the subject is liable to be altered by drugs or experimental procedure.

II. Clinical Research Combined with Professional Care

1. In the treatment of the sick person, the doctor must be free to use a new therapeutic measure, if in his judgment it offers hope of saving life- re-establishing health, or alleviating suffering.

If at all possible, consistent with patient psychology, the doctor, should obtain the patient's freely given consent after the patient has been given a full explanation. In case of legal incapacity, consent should also be procured from the legal guardian; in case of physical incapacity, the permission of the legal guardian replaces that of the patient.

2. The doctor can combine clinical research with profesional care, the objective being the acquisition of new medical knowledge, only to the extent that clinical research is justified by its therapeutic value for the patient.

III. Non-Therapeutic Clinical Research

1. In the purely scientific application of clinical research carried out on a human being, it is the duty of the doctor to remain the protector of the life and health of that person on whom clinical research is being carried out.

2. The nature, the purpose and the risk of clinical research must be explained to the subject by the doctor.

3a. Clinical research on a human being cannot be undertaken without his free consent after he has been informed; if he is legally incompetent, the consent of the legal guardian should be procured.

3b. The subject of clinical research should be in such a mental, physical and legal state as to be able to exercise fully his power of choice.

3c. Consent should, as a rule, be obtained in writing. However, the responsibility for clinical research always remains with the research worker; it never falls on the subject even after consent is obtained.

4a. The investigator must respect the right of each individual to safeguard his personal integrity, especially if the subject is in a dependent relationship to the investigator.

4b. At any time during the course of clinical research the subject or his guardian should be free to withdraw permission for research to be continued. The investigator or the investigating team should discontinue the research if, in his or their judgment, it may, if continued, be harmful to the individual.

TRAINING FOR WOMEN PHYSICIANS

A pilot study designed to evaluate a reentry into medicine course for women physicians who have been out of touch with the medical profession for ten or more years is the purpose of a contract awarded to the Presbyterian Medical Center, San Francisco, by the U.S. Public Health Service's Division of Community Health Services, Surgeon General William H. Stewart announced today.

The contract, awarded in the amount of $79,450, will allow the evaluation of a course given to six women physicians. The course will extend over a period of six months to one year.

"Approximately 16,000 female physicians are active in the medical field," Dr. Steward said. "About 2,600 female physicians are either retired or no longer in practice. Because of the need for more physicians in many parts of this country, the Presbyterian Medical Center study aims to produce a prototype program that can enable other medical centers to set up reentry courses for women physicians able and desirous of returning to active practice."

Trainees will be selected by the Presbyterian Medical Center on the basis of personal interviews and

reasonable assurance that they will engage in medical practice upon completion of the course.

The course will provide full-time training in general medicine and the medical specialties depending on the extend or previous training of the candidate. Trainees who have had general training and would like to return to general practice will be rotated in: general medicine (in-patient and out-patient services) emergency room treatment, pediatrics, minor surgery and office gynecology. Instruction will be given on the wards of the Presbyterian Medical Center, primarily in its out-patient clinics.

RADIOLOGICAL EXPOSURE

Washington, D. C. — The importance of stricter adherence to the fieldsize values recommended in hospital exposure charts of the type used routinely in the x-ray departments of many hospitals was stressed at a recent meeting of the American Roentgen Ray Society by Dr. Russell H. Morgan, Chief of the Department of Radiological Science, Johns Hopkins School of Medicine, and Chairman of the U. S. Surgeon General's National Advisory Committee on Radiation.

"One of the principal causes of unnecessary exposure in diagnostic radiology is the use of excessive field size," Dr. Morgan said, reporting the results of a 3-year study of diagnostic x-ray exposures at the Johns Hopkins Hospital, Baltimore. During this period, the levels of radiant energy received by 36,000 patients were measured while they underwent x-ray examination—an achievement that was made possible by equipping 10 of the hospital's radiographic and fluoroscopic rooms with ionization chambers and "readout" devices.

The data revealed that the fieldsize values were excessive—well beyond those needed to over standard recommended film areas—in a number of x-ray procedures, especially chest examinations. A common cause of such unnecessary exposure, it was pointed out, is negligence in collimator adjustment. Since chest x-ray are usually taken at a target-film distance of 72 inches, whereas most other films are made at a distance of 36 inches, operators performing a thoracic examination often neglect to reset the collimator after the unit has been used to x-ray other body areas.

This practice and other that result in unnecessary exposure of the patient were sharply dealt with in lectures to the medical technologists at the hospital. The need for proper beam control was also given more emphasis by radiologists and registered technologists in a supervisory position.

One of the major contributions of the study was the projection of annual genetic dose figures, based upon an analysis of the radiant-energy data gathered in the hospital sample. According to these data, gonadal exposure to x-ray averages 23 millirads annually—an amount that is considerably below the exposure resulting from background radiation.

The method by which the Johns Hopkins investigators estimate the average annual genetic dose in the general population, Dr. Morgan explained, rests on three main premises: that the amount of x-radiation absorbed by the gonads is proportional to that absorbed by the abdomen; that diagnostic x-ray techniques employed by hospitals throughout the country, whether large or small, are fairly uniform; and that persons x-rayed in the major medical centers are typical—with regard to sex, age and other characteristics—of the total x-rayed population.

The importance of taking annual estimates of genetic dosage, he said, is indicated by the general rise in x-ray diagnostic procedures, which are increasing at about 8% a year.

REGULATIONS ON SPECIAL DIETARY SUPPLEMENTS

The Food and Drug Administration has issued new regulations tightening the requirements for special diet foods and diet supplements.

The revised regulations are aimed at providing the consummer with more facts about the foods for weight control, for dietary supplementation with vitamins and minerals, and for other special diet needs, such as controlling salt intake, according to Dr. James L. Goddard, the head of FDA.

The new regulations set standards for certain foods to which nutrients may be added only if

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they have real value. A Recommended Dietary Allowances also is included as a guide to meeting nutritional needs.

The new regulations will prohibit extravagant promotion of "shotgun" multi-vitamin and mineral supplements containing nutrients that meet no dietary need and tend to deceive the consumer.

The revised labeling regulations and the new standards for fortified foods and vitamin and mineral supplements are scheduled to become effective in December.

A general revision of regulations on special dietary foods and vitamin-mineral supplements was proposed by the FDA four years ago. More than 50,000 comments were received on the provisions suggested at that time. The new regulations are the result of a review of the 1962 proposals and the comments and recommendations received about them.

Goddard said the new requirements should sweep away many of the common misconceptions about the kinds and amounts of vitamins and minerals needed in the diet, and how they are obtained. He said "most Americans eat foods that provide all the vitamins and minerals normally required for good health."

Multi-vitamin and mineral products will be required by the regulations to bear the following label:

> "Vitamins and minerals are supplied in abundant amounts by the foods we eat. The Food and Nutrition Board of the National Research Council recommends that dietary needs be satisfied by foods. Except for persons with special medical needs, there is no scientific basis for recommending routine use of dietary supplements."

The Pharmaceutical Manufacturers Association said that the new restrictions are "not in the public interest." A spokesman for the association said that when the Food and Drug Administration proposed similar regulations in 1962, "we found serious differences of opinion among nutritionists and other scientists as to the scientific basis for the proposals."

A spokesman for the National Health Federation, predicted that consumers will rebel against the regulations. He promised, "Congress will get more letters on this than on any other issue—any other." The federation is an organization of the manufacturers and distributors of unusual "health foods" and "super" vitamins.

The Drug and Allied Products Guild, composed of smaller drug manufacturers and distributors, voted authority for its officers to assess the 97 regular members up to $500 each to hire special lawyers to prepare arguments against the FDA regulations.

EMPHYSEMA AND BRONCHITIS

Two new publications on emphysema and chronic bronchitis, "Chronic Respiratory Diseases, A Growing Menace" and "Management of Chronic Obstructive Respiratory Diseases," have just been released by the Public Health Service, U. S. Department of Health, Education, and Welfare.

Emphysema and chronic bronchitis are becoming one of the Nation's most urgent health problems, as evidenced by the growing numbers of people killed and crippled by these pulmonary disorders. The number of deaths caused by these diseases has quadrupled during the last decade for which records are available, and there is no indication of any decrease in the trend. Emphysema is a crippling disease, and according to Social Security disability statistics, causes more invalidism than such well-known cripplers as cancer, stroke, tuberculosis or mental disorders.

The publications are initial efforts of the Public Health Service's recently-created Chronic Respiratory Diseases Program, which is charged with providing the medical community and the general public with the latest information on control of these diseases and with demostrating that detection, treatment and rehabilitation can help stem the potential epidemic of chronic respiratory diseases.

"Chronic Respiratory Diseases, A Growing Menace," PHS Publication No. 1445, describes the increasing significance of these diseases and outlines the functions and activities of the new PHS control program.

"Management of Chronic Obstructive Respiratory Diseases," PHS Publication No. 1457, is a resume of the Eighth Annual Emphysema Conference held in Aspen, Colorado, in June 1965. The booklet was edited by Thomas L. Petty, MD, of the University of Colorado Medical Center. The conference, sponsored by the Public Health Service, brought toge-

ther leading authorities in emphysema to discuss up-to-date methods for treatment and care of respiratory victims. The Aspen publication contains sections on definitions, respiratory failure, right heart failure and pulmonary hypertension, antibiotics and infections, home and clinic care, pharmacologic agents, and surgery.

Although many physicians are uncomfortable about providing treatment for a disease about which so little is known, participants of the conference overwhelmingly agreed that medical practitioners should be encouraged to provide proper treatment and care to the respiratory patients they are seeing in ever-increasing numbers.

Both "Chronic Respiratory Diseases, A Growing Menace" and "Management of Chronic Obstructive Respiratory Disease" are being mailed to physicians throughout the country. In addition, single copies are available from the Public Health Service, Department of Health, Education, and Welfare, Washington, D. C., 20201. The hookletsmay be purchased in quantity from the Superintendent of Documents, Government Printing Office, Washington, D. C., 20402, at 30 cents a copy, or $22.50 per 100 copies.

INTERNACIONALES

Oct. 23-29—IX International Cancer Congress. Tokyo, Japan. A charter flight and several group flights are contemplated, thus suhstantially reducing the cost of transportation. Members of the immediate family of congress participants will be eligible. Anyone interestet should communicate with Tirsch Marks, M.D., 435 East 57th Street, New York 22, N. Y.

XV CONGRESO PANAMERICANO DE TUBERCULOSIS Y ENFERMEDADES DEL APARATO RESPIRATORIO

Oct. 24-28—XV Congreso Panamericano de Tuberculosis y Enfermedades del Aparato Respiratorio, en Buenos Aires, organizado por la Unión Latinoamericana de Sociedades de Tisiología y auspiciado por la Comisión Nacional Ejecutiva del Sesquicentenario del Congreso de Tucumán y de la Declaración de la Independencia.

Las sesiones científicas tendrán lugar en la Academia Nacional de Medicina, y el Comité Organizador, que preside el doctor Raúl F. Vaccarezza, ha fijado los siguientes temas:

I. Profilaxis de la tuberculosis: quimioterapia, vacunación y quimioprotección.
II. Resultados del tratamiento en las recruscencios, recaídas y cronificación de la tuberculosis pulmonar.
III. Micosis broncopulmonares.
IV. Cáncer de pulmón: Diagnóstico y condiciones de operahilidad.

Los temas Profilaxis de la tuberculosis y Micosis broncopulmonares serán desarrollados en simposios y los dos temas restantes con presentación de relatos y comunicaciones.

La Secretaría del Congreso funciona en José Andrés Pacheco de Melo 3081.

IMMUNIZATION AGAINST TYPHOID

Surgeon General William H. Steward of the Public Health Service recently stated that routine typhoid immunization is *not* recommended in the United States. His statement was based on findings of the Public Health Service Advisory Committee on Immunization Practices. Text of the recommendations will be released July 29 in the Morbidity and Mortality Weekly Report for the week ending July 23. The Report is published by the Communicable Disease Center in Atlanta. The Committee, composed mostly of experts from without the Service, met recently at CDC.

The Committee recommended selective immunization in the following situations:

(1) Intimate exposure to a known typhoid carrier as would occur with continued household contact.
(2) Community or institutional outbreaks of typhoid fever.
(3) Foreign travel to areas where typhoid fever is endemic.

The Advisory Committee stated further, "Although typhoid vaccine has been suggested for individuals attending summer camps or those in areas where flooding has occurred, there are no data to support the continuation of these practices."

The incidence of typhoid fever in the United States has declined steadily for many years. At the present time, the Committee said, less than 500 cases are reported annually, and a continuing downward trend can be expected. Cases are sporadic and are primarily related to contact with carriers rather than to common source exposure.

Referring to vaccines for paratyphoid A and B, which are typhoid-like fevers, the Advisory Committee stated, "The effectiveness of paratyphoid A vaccine has never been established, and recent field trials have shown that available paratyphoid B vaccines were ineffective. In view of these data and recognizing that paratyphoid A and B antigens when combined with typhoid vaccine may increase the occurrence of vaccine reactions, use of paratyphoid A and B vaccines is *not* recommended."

ANUNCIOS

Comenzando con esta edición, la Junta Editora publicará anuncios pequeños del tipo de alquiler de oficinas, venta de propiedades, solicitudes de distinta índole, etc.

Si interesa anunciar algo en esta sección, favor de comunicarse con nuestras oficinas centrales. Nuestro teléfono es el 725-6969.

Bilingual (Spanish and English) physicians wanted to work in university-staffed hospital. Must be well trained in internal medicine. Salary $14,000 - $18,000 depending on qualifications. Write Department of Medicine, Lincoln Hospital, 333 Southern Boulevard, Bronx, New York 10454.

General Practitioner with some surgery experience for medical group in Los Angeles, California. United States or Puerto Rico Graduate. Starting Salary: $1,500.00 per month with partnership to follow. Contact: Dr. Raimundo Rodríguez 6538 Telegraph Road Telephone: 685-5100, Los Angeles, California 90022



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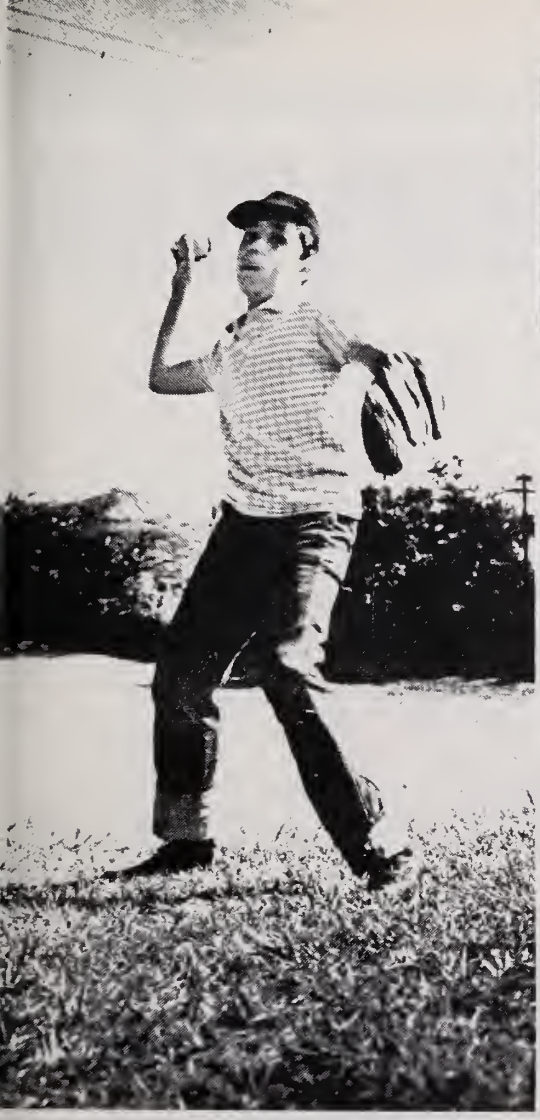
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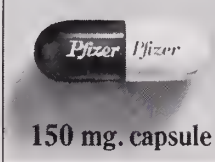
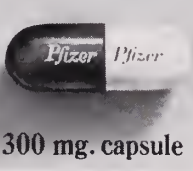
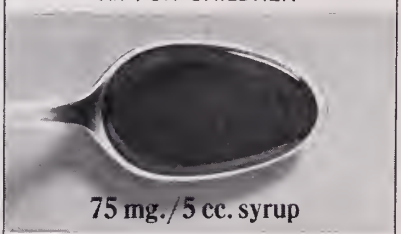
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Contraindicated: In individuals hypersensitive to methacycline.

Warning: In the presence of renal dysfunction, reduce usual oral dosage and consider serum level determinations to avoid liver damage.

Discoloration of developing teeth may occur although such toothstaining has not been reported with methacycline to date.

In certain hypersensitive individuals treated with methacycline, exposure to direct sunlight may precipitate a photodynamic reaction. Such reactions have not been reported with Rondomycin to date. In individuals with a history of photoallergic reactions to tetracyclines, exposure to direct sunlight should be avoided and treatment should be discontinued at first evidence of skin discomfort.

Precautions: As with any antibiotic, overgrowth of nonsusceptible organisms may occasionally occur. If such superinfections are encountered, Rondomycin should be discontinued and replaced by appropriate therapy.

Before treatment of gonorrhea, if concomitant syphilis is suspected, a darkfield examination should be made of any lesion and serological tests for syphilis should be made monthly for at least three months afterwards.

Increased intracranial pressure has occurred occasionally in infants treated with methacycline but has disappeared promptly and without sequelae, once therapy was discontinued.

Adverse Reactions: Glossitis, stomatitis, proctitis, nausea, diarrhea, vaginitis, dermatitis, and allergic reactions may occur rarely. If adverse reactions, individual idiosyncrasy, or allergy occur, discontinue medication.

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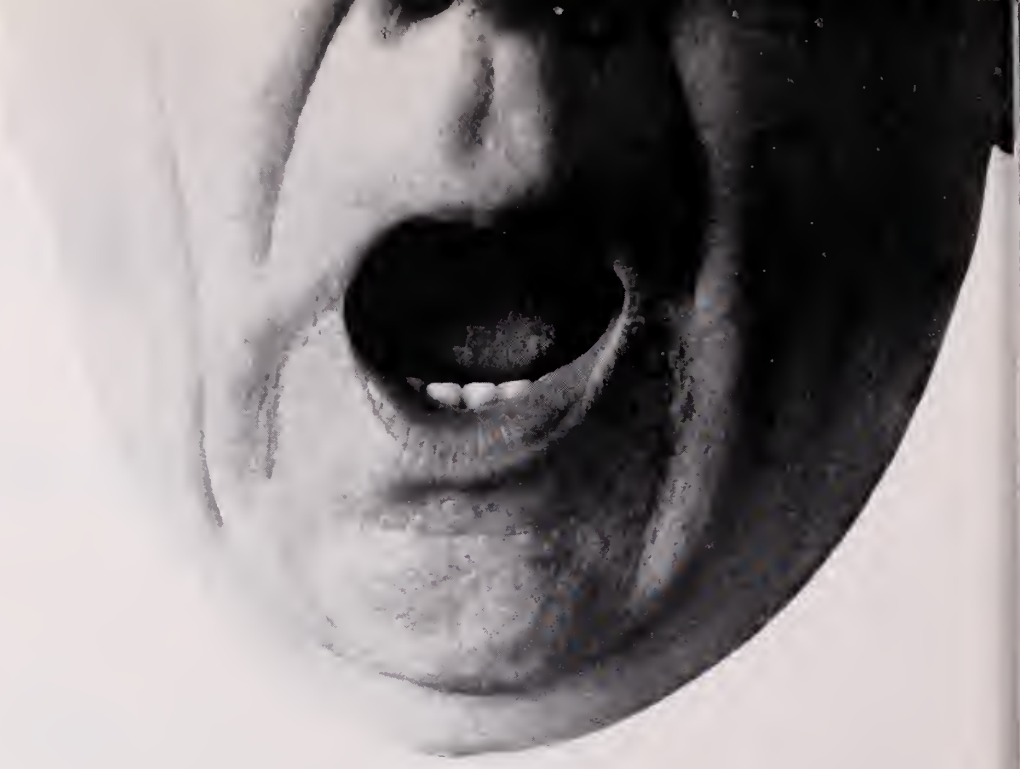
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References: (1) Blouin, L., and Overman, R. R.: Detailed reports in Mead Johnson Research Files.* (2) Gloning, K., and Klausberger, E. M.: Wien. klin. Wchnschr. *70*:145-149 (Feb. 28) 1958. (3) Whittier, J. R., and Dhrymiotis, A. D.: Angiology, *13*:324-327 (July) 1962. (4) Horton, G. E., and Johnson, P. C., Jr.: The Application of Radioisotopes to the Study of Cerebral Blood Flow and the Effects of Isoxsuprine (to be published). (5) Horton, G. E., and Johnson, P. C., Jr.: The Application of Radioisotopes to the Study of Cerebral Blood Flow, Comparison of Three Methods, Angiology, (to be published). (6) Whittier, J. R.: Vasorelaxant Drugs and Cerebrovascular Disease, Angiology, (to be published). (7) Dhrymiotis, A. D., and Whittier, J. R.: Current Therap. Res. *4*:124 129 (April) 1962.

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RESUMEN: ACCION E INDICACIONES: Una sola dosis de IMFERON (inyección de hierro dextrán) produce una alza apreciable de la hemoglobina y una serie completa de inyecciones restituye efectivamente los depósitos de hierro. El IMFERON está indicado únicamente en casos diagnosticados de anemia ferropriva, en los que resulta inefectiva o poco práctica la administración de hierro oral. Tales deficiencias de hierro pueden incluir: pacientes en el último trimestre de gestación; pacientes con trastornos gastrointestinales o en vías de recuperación de intervenciones quirúrgicas del tracto gastrointestinal; hemorragias crónicas con pérdidas de hierro continuas y masivas que no responden rápidamente al hierro oral; pacientes refractarios a transfusiones como fuente de hierro; niños con anemia hipocrómica; pacientes en quienes no se puede confiar que tomen hierro oral.

COMPOSICION: El IMFERON (inyección de hierro dextrán) es una solución bien tolerada de complejo de hierro-dextrán que proporciona el equivalente a 50 mg. de hierro elemental por cada cc. La solución contiene 0.9% de cloruro de sodio y su pH varía entre 5.2 y 6. El frasco-ámpula de 10 cc. contiene 0.5% de fenol como preservativo.

ADMINISTRACION Y POSOLOGIA: La dosis, basada en el peso corporal y gramos de hemoglobina en 100 cc. de sangre, varía desde 0.5 cc. para lactantes hasta 5 cc. para adultos, aplicada diariamente, en días alternos, o semanalmente. El requerimiento total en cada individuo es fácilmente determinado mediante la tabla de dosificación contenida en el prospecto. La inyección intramuscular profunda en el cuadrante superior externo de la región glútea, empleando la técnica trayectoria en Z (con desplazamiento lateral de la piel, previo a la inyección), asegura buena absorción y evita la coloración de la piel. Se recomienda una aguja de por lo menos dos pulgadas de largo para el adulto normal.

EFECTOS SECUNDARIOS: La incidencia de efectos secundarios sistémicos y locales es poco común. Puede ocurrir coloración de la piel. Una dosis excesiva, superior a la requerida, puede producir hemosiderosis. A pesar de que las reacciones alérgicas o anafilácticas son rarísimas, se han presentado ocasionalmente reacciones serias; tres reacciones fatales han sido atribuidas al IMFERON (inyección de hierro dextrán). Raras veces se ha reportado urticaria, artralgia, linfoadenopatía, náusea, jaqueca y fiebre. Se recomienda aplicar inicialmente una dosis de prueba de 0.5 cc.

PRECAUCIONES: Si hay reacción de sensibilidad a la dosis de prueba no deberá administrarse el fármaco. El IMFERON (inyección de hierro dextrán) deberá administrarse únicamente por vía intramuscular profunda. La inyección deberá solamente aplicarse en el cuadrante superior externo de la región glútea, y no en el brazo u otras áreas. El riesgo de carcinogénesis en seres humanos es insignificante cuando se emplea el IMFERON (inyección de hierro dextrán) en la forma recomendada.

CONTRAINDICACIONES: El IMFERON (inyección de hierro dextrán) está contraindicado en pacientes con sensibilidad comprobada al complejo de hierro dextrán. Por estar destinado exclusivamente a la terapia de las anemias ferroprivas, no deberá utilizarse en el tratamiento de otras anemias.

PRESENTACION: Ampulas de 2 cc. cajas de 10; ámpulas de 5 cc. cajas de 4; frasco-ámpulas de 10 cc. de dosis múltiple.

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THE RADIOACTIVE KIDNEY FUNCTION TEST: CLINICAL USES AND LIMITATIONS

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The radioisotope renogram has been presented repeatedly in the medical literature as a screening test for hypertensive patients in the search for cases of unilateral hypertensive renovascular disease. (1-17) The value of the renogram as derived from this particular clinical application has been, in our opinion, over-emphasized.

The purpose of this report is to present experiences and conclusions on the uses and limitations of the radioactive kidney function test gathered throughout a six year period at the Radioisotope Unit of the San Juan City Hospital. We will emphasize observations which demonstrate the value of the test in the study of clinical conditions commonly encountered in the everyday practice of medicine. We are also particularly concerned in presenting an objective definition for the normal renogram.

Material and Method

Four hundred and thirty seven subjects were studied including ninety-four subjects without history or evidence of renal disease or hypertension. The latter group included members of hospital personnel, student nurses, blood donors, hospitalized and ambulatory patients. The sex distribution in this control group was 42 males and 52 females. The average age for the whole group was 38 years; 39 years for the females and 36 years for the males. The ages ranged from 13 to 72 years. Only 4 subjects were beyond 70 years, 16.2% of the whole group were older than 50 yrs. and 3.8% below 20.

Over fifteen hundred tracings obtained from tests performed in 343 patients with a wide variety of renal diseases and other clinical conditions, were studied and correlated with the clinical status including other laboratory and radiological studies.

Subjects were instructed to drink adequate amounts of fluid the day of the test. As soon as they arrived at the Radioisotope Unit they were asked about their recent liquid intake and were encouraged to drink two or three glasses of water one hour prior to the test. No attemp was made to control the liquid intake but as regards preparation of subjects for the test we were only interested in assuring adequate hydration. Our kidney function unit consists of paired scintillation detectors (Nuclear Chicago's DS 5-2) with 1 x 1 in. crystals and a 1 in. lead shield which projects 4 cm. beyond crystal. Each scintillation probe is connected to its respective ratemeter provided with a rectilinear chart recorder. The systems were carefully checked for the zero and calibration levels as well as the sensitivity with a source of radiation.

The test was performed using the 30K scale and the 10 seconds time constant. The speed of the chart recorder used was 6 in/hr. The subject was asked to empty the bladder immediately before the test. Unless X rays films taken in the standing position showed malposition of kidneys, the right probe was placed tight to the skin and tangential to the 12th rib along the lateral border of the

From the Radioisotope Unit and the Department of Medicine, San Juan City Hospital, and the Nuclear Medicine Laboratory, Hospital Pavía, San Juan, Puerto Rico.

erector spinae mass with the subject in the sitting position. The left probe took a similar position 1½ in. higher than its mate. Standing behind the left side and holding the subject firmly with the left hand it is useful to press with the right thumb between the probes to palpate the spine and check that the probes are not displaced to either side. It is also very practical to ask the patient if he feels the probes equally tight.

Another method of determining the position of the probes is the use of a small "monitoring dose" of about 5 uc, setting rate meters to a lower scale and faster time constant and searching for the point of maximal radioactivity after the intravenous injection of the dose. We have seldon used this method hut it may be useful in special cases. A variant of the latter method is to proceed similarly at the end of the test moving the probes up and down the ratemeter set at a fast time constant and checking whether the probes were indeed at the point of maximal radioactivity.

The dose of I ^{131} - orthoiodohippurate* used approximated 0.05 uc/kg of body weight. With experience one can tell the dose required without calculations from just looking at the size and frame of the patient. The only important thing about the dose is that it should be enough to give a tracing of adequate amplitude and confined to the limits of the chart on the selected scale of 30K. After the position of the probes has heen determined and fixed, the labeled hippurate is injected intravenously through the antecubital vein.

An important aspect of this study was to define with some ohjectivity the normal renogram. For doing this, 208 renographic curves obtained from the 94 control subjects were studied. For this purpose we considered each renographic tracing separately. Our method of studying the curves coincides with that reported by Boy and Murdock (18). The distance from the begining of the tracing to the maximum peak measured along the horizontal was determined in all renograms. Knowing the speed of the chart, the time for maximum peak (Tp) to appear was determined. Other measurements included the maximum or peak height (Hp) and the twenty minutes height ($H_{20''}$). The ratio of the twenty minutes height to the maximum height expressed in per cent was likewise determined and we refer, to this value as the twenty minutes renographic index (20" R. I.).

Test of renal function including the 15 minutes PSP excretion, urea clearance and the Fishberg's concentration test were performed by standard methods.

Timed urine specimens were not collected except in cases with doubtful state of hydration for the only purpose of confirming an adequate urine flow. Quantitative analysis of radioactivity excreted in the urine were not done. In occasional patients with nephrostomy,, differential studies with the urine were performed.

Results

I. The Normal Renogram

1. *Time peak* (Tp)

The time elapsed from the begining of the tracing to the peak height (Tp) varied from 1.8 to 7.5 minutes. The average Tp value for the whole group was 3.1 minutes. In only 4.3% of the tracings was the Tp longer than 5 minutes. The shortest time for Tp was 1.8 minutes with 7.7% of the renograms within the narrow range of 1.8 to 2 minutes.

On second tests performed in four patients showing one renographic tracing with Tp value over 5 minutes, the Tp was less than 5 minutes in all.

2. *The twenty minutes renographic index*— $\frac{H_{20''}}{H_p} \times 100$

The 20"R.I. values varied from 12 to 36%. Only 2% of the renographic tracings showed 20"R.I. values higher than 35% while 2% were below 15% with 90% of the renograms showing 20" R.I. values between 15 and 33%. The average 20"R.I. value for the whole group was 24%.

* *Squibb's Hipputope and Abbott's Hippuran.*

3. *Differences between right and left renograms*

Differences in amplitude or peak height (Hp) between right and left renograms were evident. Miscalibration of the systems as the cause of these differences was excluded in all cases. In only two tests the amplitude of the two tracings was exactly identical. To study the magnitude of those differences, the Hp of the smaller tracing was expressed as a per cent of the Hp of its mate renogram.

The results showed that in 90.4% of the tests, the smaller renogram had an amplitude greater than 85% of its mate tracing with an average value of 92%.

Differences in the 20"R.I. values between the right and left renograms were also observed and averaged 5% for the whole group. In 4% of the tests the difference was more than 8%.

Discussion

The use of radioactive compounds for the study of renal function, using external radiation detection and recording techniques, was first reported in 1956 by Taplin and Winter, (1). The test described provided graphic records of the radioactivity over each renal areas after the intravenous injection of a radioiodine labeled sustance selectively excreted by the kidneys. It was proposed that the tracings obtained presented separate information on the vascularity, tubular function and patency of the urinary outflow tracts.

Of all agents tested, I-131 - orthoiodohippurate is today generally accepted to be the best because of its rapid excretion by the kidneys and the fact that there is no significant liver uptake which could modify the right kidney tracing.

The test has been referred to by such names as the radioactive kidney function test, the radioisotope renogram or nephrogram and Winter's test as it was C. C. Winter who made the pioneer work on its clinical applications, (2).

The evident variables of the dose, the positional factors, state of hydration and urine flow initially discouraged the consideration of the renographic pattern as a reliable measure of renal function.

It is concluded from the evidence presented, that the normal renogram is a tracing characterized by an initial segment which is followed by an ascending segment which reaches peak height within a period of 2 to 5 minutes. The height of the renographic tracing will decrease progressively to reach a level of 15 to 33% of the peak height, two inches from the initial deflection corresponding to a 20 minute period. An illustrative example of a normal renogram is shown in Fig. 1.

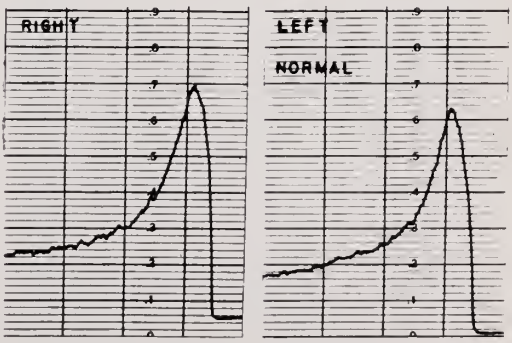


Fig. 1: The renographic tracings are recorded from right to left. These are bilateral normal renograms. The distance between vertical lines actually measures 0.75 inch and corresponds, at the speed of recording, to a 7.5 minutes period.

In terms of our method of study the normal renogram should fulfill the following criteria:

1. *Time peak*: The maximum height should be reached within 2 to 5 minutes.
2. *20" R. I.*: The 20 minutes height should be 15 to 33% of the peak height.
3. *Difference in Hp*: The smaller tracing should have 85% Hp or more that of its mate renogram.

If these criteria are not fulfilled, the subject should have repeated tests to prove reproducibility of abnormal findings. When the amplitude (Hp) of one tracing is less than 85% of its mate but is otherwise normal, miscalibration of the systems and positional factors should be at once suspected and excluded. Differences in amplitude are particularly significant, suggesting renal dysfunction, when they are associated with decreased steepness of what has been referred to as the functional segment. The functional segment is the part of the tracing which follows the maximum peak. The steepness of this segment depends upon adequate circulatory delivery, tubular transport and excretion of the radiohippurate.

In comparing our definition of the normal tracing with that of Boyd and Murdock, (18) our lower value of 33% for the upper normal limit of the 20" RI, as compared to their reported value of 40%, is readily explained by the fact that our normal group was considerably younger. This was predicted by these authors.

The reason for selecting 20 minutes as the time for measurements is to avoid falsely elevated values for the renographic index, if measured at 10 or 15 minutes, due to early unpredictable excretory irregularities which may normally occur.

The initial segment of the renogram is the result of the arriving initial bolus of radioactivity to the great vessels, the kidney and neighboring organs. After this initial deflection, the progressive increase in radioactivity is due to active concentration of the labeled hippurate by the kidney, a function of the renal tubules (19). This active tubular transport of the labeled agent will built up the radioactivity within the kidney to the peak value reached within 2 to 5 minutes in the normal subject. When the amount of radioactive hippurate excreted in the urine and leaving the kidney to the bladder is greater than the amount being removed from the circulation, the radioactivity over the renal areas will decrease within the range of 15 to 33% of the maximum level of radioactivity, 20 minutes after the arrival of the labeled agent to the kidney.

It is of crucial importance that the patient preserve the position and geometrical relations to the system throughout the 20 to 30 minutes period which the test ordinarily lasts. Some patients tend to slip slowly and steadily forward. The decreasing radioactivity due to the progressive movement of the kidneys away from the probes will simulate excretion in the renographic tracings.

Some investigators (20) attempt to control the state of hydration and consequently the urine flow by preparing subjects with restriction of fluids and other measures. In this respect, we are only concerned in excluding dehydration allowing liberal intake

of liquids. This may be important in the sick hospitalized patient. Ambulatory subjects do not, in their ordinary activity, allow themselves to become dehydrated. Our arguments for proceeding this way are that the variables of state of hydration from patient to patient and urinary flow from patient to patient and perhaps from kidney to kidney in the same patient cannot be completely controlled. Furthermore we are convinced that the sick kidney will not improve its function with water loading.

The quantitiation of the amount of radioactivity excreted in the urine is unnecessary. The information is no better than that of a routine PSP excretion test. The use of other radiation detectors over the urinary bladder, the heart or elsewhere is a likewise unnecessary complication of the procedure. No matter how many detectors and how many additional tracings, the renograms will give the critical information.

The hazards of radioactivity in the test must be considered minimal. The amount of radiation received during a test is less than 1/1000 that received during a chest roentgenogram (21). The dose of radioiodine involved in the procedure compares with that used in routine thyroid uptake studies. This dose is bound to the hippuric acid salt and the amount of the latter is in the order of micrograms. In the normal subject 80% or more of the dose reaches the urinary bladder within a period of 90 minutes. In no other clinical diagnostic procedure involving radioactive iodine will the radioisotope be excreted faster than in the radioactive kidney function test. We have never encountered any allergic or other type of undesirable side effect from the injection of the agent.

Any pathological process affecting the renal plasma flow, the effective delivery of the hippurate through the renal vascular apparatus to the renal tubules, the effective tubular handling of the hippurate or the patency of the urinary tract can cause an abnormal renographic pattern. On the other hand, any renal condition sparing the three levels mentioned can show a normal pattern. An example of the latter is diabetes insipidus and probably other conditions with selective metabolic tubular deffects. We have never had a case shown to have renal insufficiency by the conventionally used renal function tests showing renographic tracings fulfilling our criteria for the normal. If at any time, such situation is shown to occur in a single case, our conclusions will be invalidated.

The most common extrarenal conditions known to secondarily modify the renogram are: dehydration, congestive heart failure, obstructive uropathies and vasomotor phenomena. A renogram is called abnormal on the basis of intrinsic renal disease, if in the absence of these conditions the tracings fail to fulfill the criteria for the normal. It cannot be overemphasized that the abnormal pattern must prove to be reproducible on repeated tests. A single test with abnormal renographic patterns is usually meaningless unless the validity of the abnormal findings has been confirmed subsequently.

We are using the following functional classification of abnormal renographic patterns based on our present experience and preliminary observations:

Class I — *Decreased renal functional reserve*

The class I renographic pattern (Fig. 2-a) is the closest to the normal. This pattern is characterized by decreased steepness of the functional segment. In our working terminology the class I renogram shows a 20" RI definitely above the normal.

We have, rather frequently, seen this type of tracings in apparently normal elderly subjects, in young hypertensives and in diabetics. The class I renogram is always correlated with normal values in all of the conventional tests of renal function.

Boy and Murdock (18) reported this type of pattern in normal elderly subjects showing normal values in other renal function tests. It is of interest to recall the studies of Davies and Shock (22) on the physiology of the aged kidney which revealed decreased glomerular filtration rate as well as renal plasma flow with the consequent diminution in renal functional reserve. The old kidney may eventually show impaired ability to concentrate urine. These abnormalities result from the progressive anatomical exclusion of functional renal tissue due to the progressively decreasing renal blood flow.

Therefore we feel that it is reasonable to assume that the class I renographic pattern, wheather seen in an elderly patient, a diabetic, a hypertensive or in any other renal condition, indicates decreased renal functional reserve which escapes detection by the usual clinical tests of renal function.

Class II - *Loss of functional reserve or early renal insufficiency.*

The class II renogram is further from the normal pattern. As compared with the previously described abnormal pattern, the class II tracing shows (Fig. 2-b) not only delayed excretion of the labeled hippurate but also decreased uptake resulting in widening and blunting of the curve.

Other test of renal function start to show abnormal values although not necessarily all of them. This type of tracing we feel, represents advanced or in some cases total loss of the renal functional reserve or even early renal insuficiency demonstrable by conventional tests.

This pattern is frequently observed in patients with prolonged history of severe hypertension, long standing diabetes with urinary abnormalities, chronic pyelonephritis and chronic glomerulonephritis.

Class III - *Advanced renal insufficiency*

This pattern (Fig. 2-c) shows minimal or no concentration of the I ^{131} labeled hippurate beyond the initial deflection. Some excretion is still present. Patients with the bilateral pattern will, of course, show very abnormal values in all function tests with the not infrequent exception of the blood urea nitrogen.

Class IV - *Terminal renal insufficiency*

This is the straight horizontal pattern (Fig. 2-d) denoting almost total inability for detectable concentration and excretion of the labeled hippurate. It is the renographic pattern of non-functioning kidney. As it is also seen at the site of nephrectomy we often refer to the class IV tracing as the pattern of "absent kidney".

All 23 patients with bilateral class IV patterns showed azotemia or uremia. None of the cases have so far survived longer than a

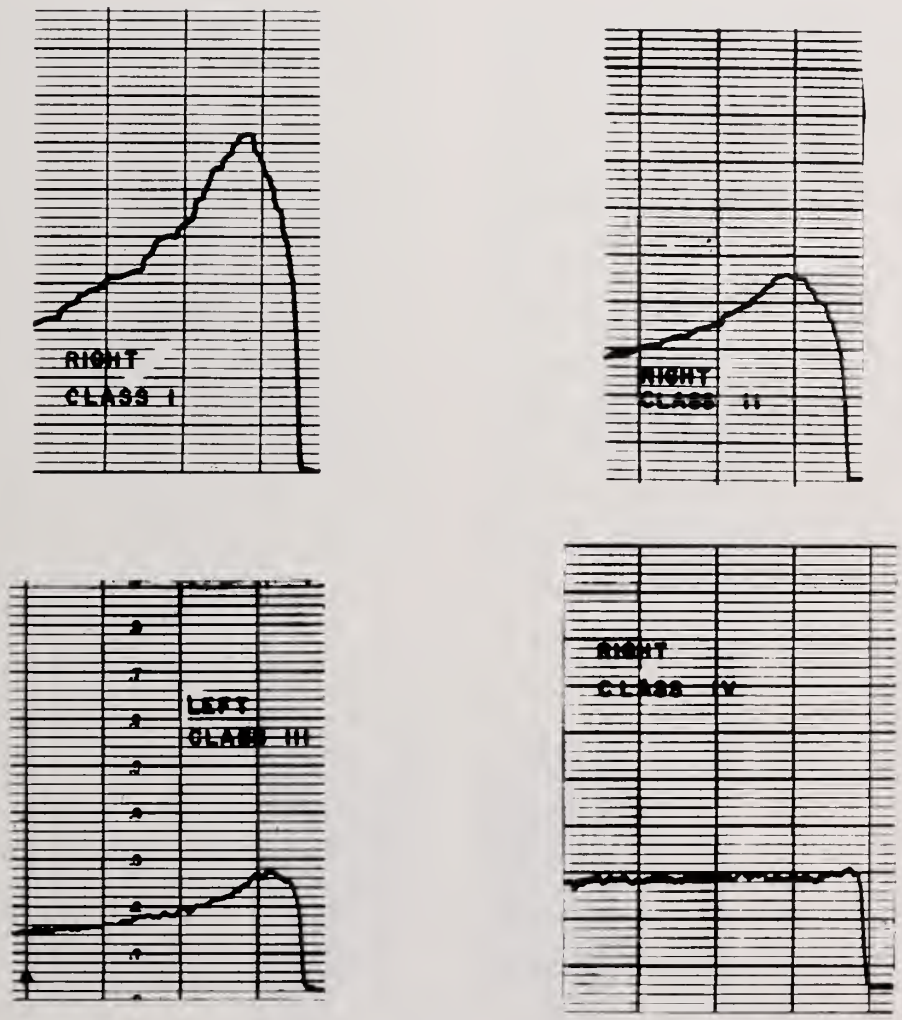


Fig. 2: Illustrative examples of renograms classified according to our proposed functional classification.

year. Eleven autopsies in this group showed small contracted kidneys of chronic pyelonephritis, chronic glomerulonephritis or nephrosclerosis.

It must be stressed that the patterns described are not specific of any particular renal disease. They just represent normal function or varying degrees of renal dysfunction the etiology of which must be searched for by other means.

These patterns do not have to be shown bilaterally, for unilateral or asymmetrical renal pathology is a frequent occurrence. Figure 3 illustrates an example of a unilateral class II tracing due to a right contracted kidney with chronic pyelonephritis, a common cause of unilateral renal disease. The left tracing fulfills our criteria for nor-

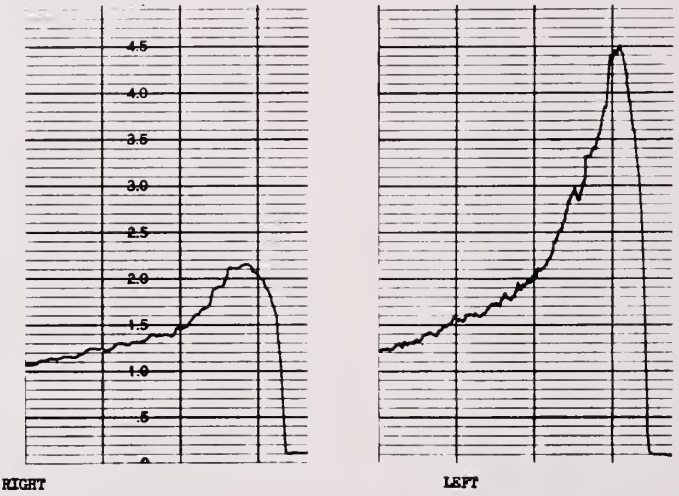




Fig. 3: Renogram and intravenous pyelogram from a patient with a right contracted chronic pyelonephritis. The left renographic tracing fulfills our criteria for the normal.

mal. Another example of unilateral renal disease is shown in Fig. 4, a case, of left renal tuberculosis. Fig. 5 illustrates a unilateral class IV tracing associated with a left non-functioning hydronephrotic kidney.

The straight horizontal tracing was not the only renographic pattern associated with terminal renal disease. The renograms shown in four terminal cases with the nephrotic syndrome, denote preserved ability for concentration of the hippurate but very delayed excretion simulating obstruction. At autopsy one of the cases showed chronic glomerulonephritis while another presented the pathological picture of systemic lupus erythematosus. This same pattern was observed in other patients with acute glomerulonephritis, Weil's disease with renal involvement manifested by hematuria, albuminuria and azotemia, systemic lupus erythematosus, Amphotericin B toxic nephropathy, and a case of the socalled Henoch-Schonlein nephritis proven at autopsy to have an acute systemic necrotizing vasculitis with very severe diffuse renal involvement. This same "pseudoobstructive" pattern is most frequently observed in dehydrated patients and in congestive heart failure. An example of renographic findings in congestive heart failure is presented in Fig. 6. This patient was admitted in heart failure due to hypertensive cardiovascular disease. The initial renograms (Fig. 6-a) show bilateral pseudoobstructive patterns which reverted after compensation (Fig. 6-b). It was observed that the left tracing consistently presented a smaller amplitude and evident decreased uptake and excretion of the radiohippurate as compared with its mate tracing. These findings were shown to be due to unsuspected left renal disease with neophrolithiasis (Fig. 6-c).

The best established and least controversial clinical application of the radioactive kidney function test is perhaps its use in obstructive uropathies. The renographic findings in two patients with obstructive uropathies due to right ureteropelvic stenosis and left nephrolithiasis are shown in Figures 7 and 8 respectively.

The renogram is very useful in cases with bilateral obstruction of the urinary outflow tracts as it provides differential information of residual renal function. This is important, because of the phenomenon of renal counter-balance, for the planning of surgery. Such a situation is illustrated by the tracings (Fig. 9) which examplify the findings in a case with bilateral ureteral obstruction due to carcinoma of the cervix. The left renogram shows a class IV tracing associated in this case with a non-functioning hydronephrotic sac, the eventual outcome of chronic unrelieved obstruction. The right tracing denotes fairly good concentration of the radiohippurate by the radiographically classified grade III hydronephrotic kidney.

The renogram may be, under particular circunstances, the only clinical procedure that can provide information on individual kidney function. This is so in patients with azotemia who can not have intravenous pyelography or in patients who are too ill to undergo cystoscopy with ureteral catheterization for differential studies. One such situation is this of an elderly female with polycystic kidneys who developed massive hematuria. Cystoscopy showed the blood was coming from the right urinary tract. Surgery was inmediately considered but discarded when the renogram (Fig. 10) revealed the left kidney function was extremely poor.

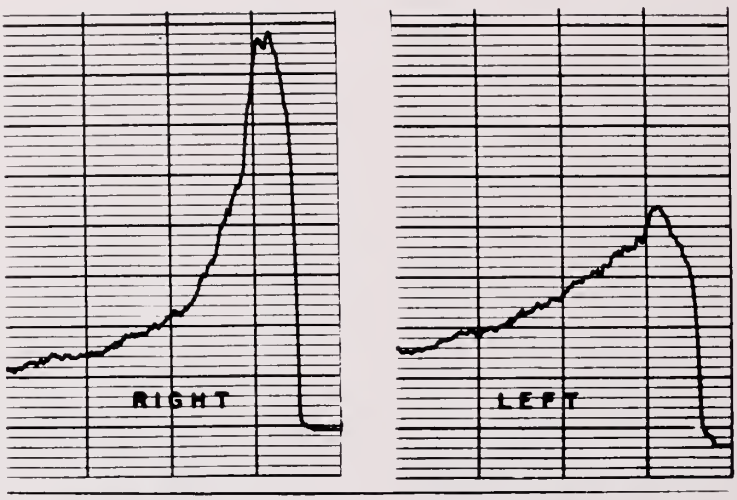




Fig. 4: Radioisotope renogram denoting marked difference in function between both kidneys. This is an example of unilateral renal disease due to left renal tuberculosis. The retrograde pyelogram shows the anatomical changes responsible for the functional deficit.

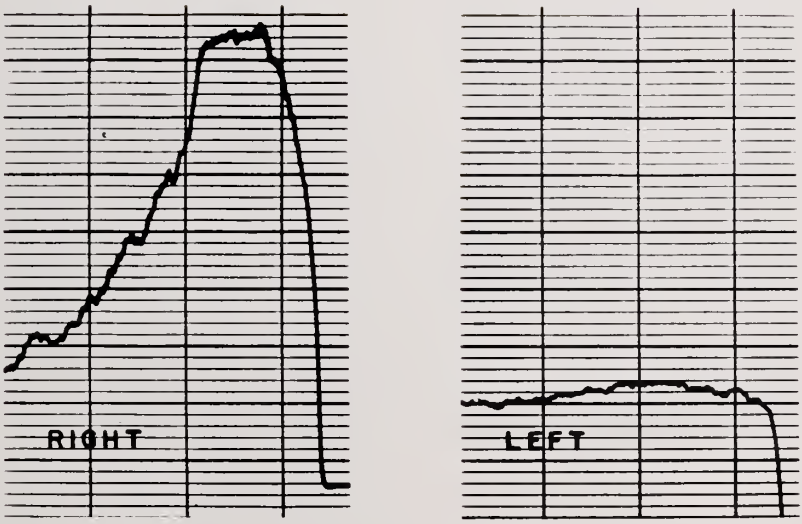
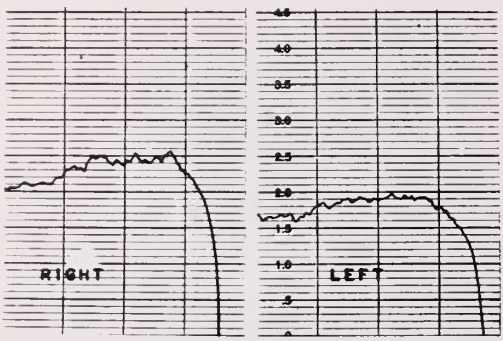




Fig. 5: Renographic tracings in a patient with a left non-functioning hydronephrotic kidney. The retrograde pyelogram was attempted and the catheter reached a blind sac.



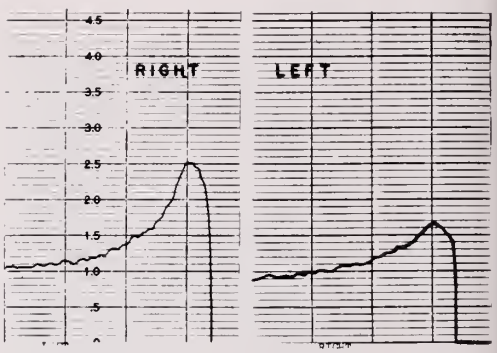


Fig. 6: a) Pseudo obstructive renographic patterns in a patient with congestive heart failure.

b) Renograms in the same patient after compensation. The changes shown on left tracing of decreased amplitude and delayed uptake and excretion of the radiohippurate suggested the possibility of local disease on left kidney responsible for the difference in function.



c) Flat film of the abdomen disclosed left nephrolithiasis.

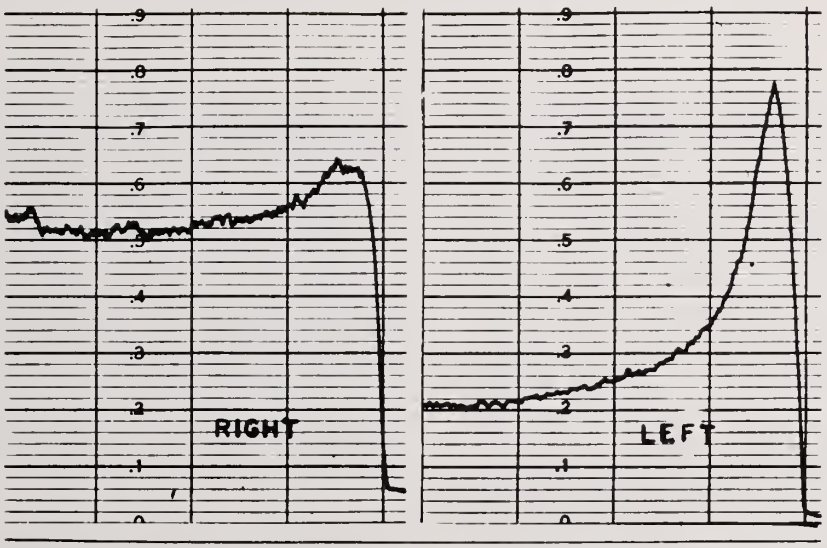




Fig. 7: Renographic tracings and retrograde pyelogram in a case with right ureteropelvic stricture.

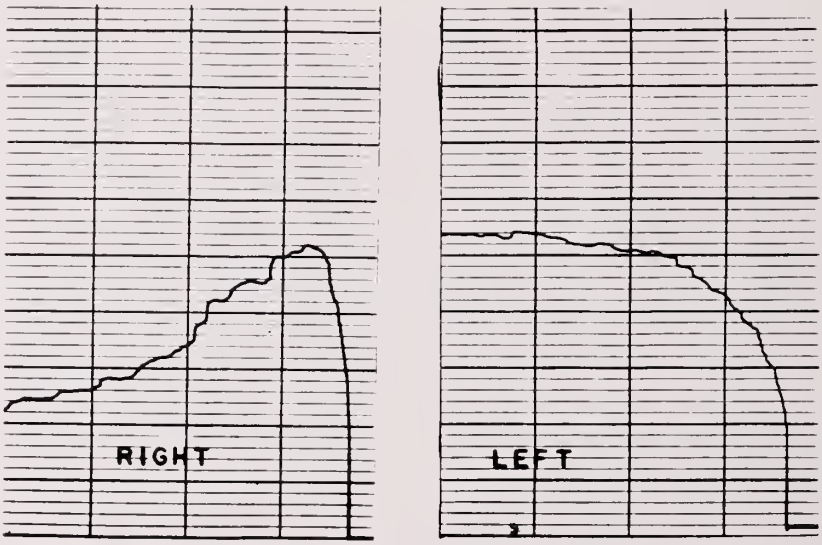




Fig. 8: Renographic tracings and IVP in a case with complete obstruction of the left urinary outflow tract at the region of the ureteropelvic junction due to a large calculus (arrow).

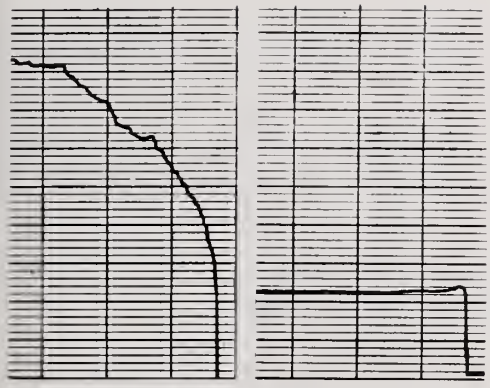




Fig. 9: Renographic tracings and IVP from an elderly female with advanced carcinoma of the cervix and bilateral obstruction of the urinary outflow tracts. The right renogram presents an obstructive pattern and was correlated with a grade III hydronephotic right kidney in the IVP. The left renogram shows a class IV pattern; the IVP showing no detactable concentration of the radioopaque dye.

Particularly promising are our recent observations with collagen diseases. We have observed reversal of the pseudoobstructive renographic pattern after steroid therapy, worsening after withdrawal and again improvement with a second course of treatment.

Another important observation is the worsening of the renographic pattern of hypertensive patients induced by aggressive treatment. It is suggested that the renogram may be of help for determining optimal antihypertensive therapy which will not jeopardize residual renal function.

We have evidence suggesting that the renogram is a very sensitive test for the follow-up of toxic nephropathies. The marked abnormalities shown in serial renograms in two patients receiving Amphotericin B for cryptococcal meningitis, in the abscence of azotemia were surprising. The findings correlate well with the report of Iovine et al (23) who were impressed by the evident and long lasting glomerular and tubular

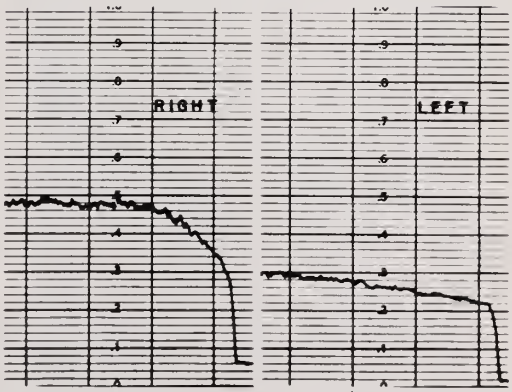


Fig. 10: Renographic tracings from a patient with polycystic kidneys and severe hematuria shown by cystoscopy to originate in the right upper urinary tract. The findings discouraged surgery because of the poor function of the left kidney shown by renography.

morphological abnormalities shown in renal biopsies from patients receiving this drug who did not have azotemia.

The value of the renogram does not reside on its use as a screening test for the hypertensives on the search for the academically glamorous cases with unilateral hypertensive renovascular disease. This most emphasized use of this test, is in our opinion, the most controversial and least reliable. The inevitable positional uncertainties in the placement of the detectors over the kidneys, gravitate most critically towards invalidation of findings, in these cases. The radiorenogram is an excellent screening test, but a screening test for unilateral or bilateral renal dysfunction and capable of detecting renal dysfunction even at its early stages.

We feel that the most common application of the radioactive kidney function test will be its use by the clinician, in the everyday practice of medicine, to know whether a hypertensive, a diabetic or any other type of patient with presumptive renal disease, shows intact or decreased renal function. Not infrequently the test, by providing differential information, will lead to the discovery of unsuspected bilateral or unilateral renal dysfunction and among the latter cases, renovascular disease may eventually be demonstrated.

On the light of our present experience the renogram has come to stay as an important clinical procedure which provides the clinician separate and faithful portraits of renal function.

Summary

A report on the clinical uses and limitations of the radioactive kidney function test is presented. The authors establish their criteria for the normal renogram. A functional classification of adnormal renographic tracings is suggested.

Renographic tracings in several conditions are shown to illustrate important clinical applications of the radioisotope renogram. The value of the renogram as a screening test for unilateral or bilateral renal dysfunction is emphasized.

Resumen

Se presenta un informe sobre los usos clínicos y las limitaciones del renograma radioisotópico. Los autores establecen los criterios para el renograma normal. Se sugiere una clasificación funcional para los renogramas anormales.

Trazados renográficos en una variedad de condiciones son presentados para ilustrar importantes aplicaciones clínicas del renograma. Se enfatiza el valor del renograma como prueba de cedazo para disfunción renal unilateral o bilateral.

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RENOGRAPHIC STUDIES IN LUPUS ERYTHEMATOSUS

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Lupus erythematosus is a disease known for over 130 years (1). It was Cazenave (2) who first coined the term "lupus erythematodes". Kaposi (3) in 1872 was the first to adequately describe the constitutional symptoms of the disease, and Osler (4) correlated the dermal manifestations with visceral involvement.

Renal involvement was first recognized at the turn of the century (1). In 1922 Keith and Rowntree (5) reported four cases of lupus erythematosus with renal involvement and stated that "Nephritis was a common complication of the disease". During the past two decades great interest has developed in the study of this disease, to a large extent attributable to the excellent pathologic description by Klemperer (6) and to the discovery of the L.E. cell by Hargraves (7). The outstanding renal manifestation of the disease have been emphasized by Muehrcke, Kark, Pirani, and Pollak (1). They stimulated our interest in this aspect of the disease.

The study of new avenues of investigation was undertaken two years ago by our group. Emphasis has been given to the use of the radioisotope renogram in the study of these patients.

The use of radioactive compounds for the study of renal function was first reported by Taplin and Winter in 1956 (8). Using external radiation detection and recording techniques, these authors described a test which provided graphic records of the radioactivity over each renal area after the intravenous injection of a radio-iodine labeled substance selectively excreted by the kidneys. They proposed that these tracings provided differential information on the vascularity, tubular function and patency of the urinary outflow tract. In a previous report we stressed the value of the test in the study of a wide variety of clinical conditions with presumptive renal involvement (9).

It is the purpose of this paper to report preliminary observations on the value of the radioisotope renogram in the detection and grading of renal involvement, the evaluation of therapeutic response, and its potential prognostic value in lupus erythematosus.

Material and Methods

A diagnosis of systemic lupus erythematosus has been established in 56 cases during the past five years using the point system devised by Nickel and Rupe (10). Of these, thirty eight patients or 68% were found to have some type of urinary

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abnormality (Table I). Thirty seven of the thirty eight patients had persistent albuminuria, twenty five had hematuria, twenty seven had pyuria, nine had evidence of a nephrotic syndrome and sixteen showed definite azotemia. All of these patients were considered to have lupus nephropathy.

These findings compare favorably with those reported in other large series of cases where the incidence of renal involvement has been between 49 and 80% (11). Our criteria for a diagnosis of lupus nephropathy have been those utilized by other authors and include: persistent albuminuria, persistent hematuria, azotemia and nephrotic syndrome (11). We excluded hypertension, as this has been observed infrequently and exclusively in patients with definite evidence of renal failure and/or receiving large doses of corticosteroids.

During the past two years, fifteen of these cases have been subjected to renographic study. In their evaluation, a series of renal function studies has been utilized, that include urinalysis, blood urea nitrogen, urea clearance, 15 min. P.S.P. excretion, concentration tests, bacteriologic study of the urine, and 24 hour protein excretion. On the basis of these studies, we have classified our patients into three groups:

Group I—Patients with normal renal function studies.

Group II—Patients with definite abnormalities in renal function studies.

Group III—Patients with severe abnormalities in renal function studies and the clinical picture of nephrotic syndrome.

The radioisotope renograms were performed following the procedure previously reported by us (9).

TABLE I: RENAL INVOLVEMENT (56 cases)

Renal Manifestation	No. of Cases	Percentage of total
Any	38	68
Albuminuria	37	66
Hematuria	25	45
Pyuria	27	48
Nephrotic syndrome	9	16
Azotemia	16	29

Results

Group I—Six of the fifteen patients were included in this group. All had persistently negative urinalysis during prolonged periods of observation. The renographic pattern was normal in four of them, and abnormal in two.

Fig. 1 shows the normal renographic pattern of Case 1, a 34 yr. old white female

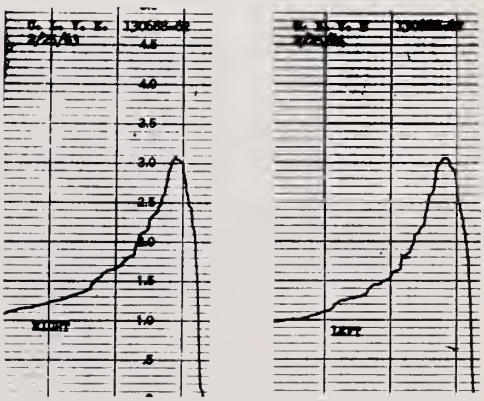


Fig. 1, Case 1: Normal renal function tests, normal renogram.

with systemic lupus erythematosus manifested by rheumatoid like arthritis, recurrent urticaria, lymphadenopathy, splenomegaly, leukopenia, thrombocytopenia, hyperglobulinemia, elevated erythrocyte sedimentation rate, positive latex test for rheumatoid factor and positive L.E. cell preparation.

Repeated urinalysis were negative except for ocassional white blood cells. The BUN was 10 mgm/100 ml., and urea clearance 92%. Concentration tests showed a maximum specific gravity of 1.024. The P.S.P. test showed 35% excretion in 15 minutes.

Fig. 2 shows the abnormal renographic pattern of Case 5, a 15 year old white girl with systemic lupus erythematosus manifested by arthralgias, fever, weight loss, butterfly rash, Coombs negative hemolytic anemia of 6.8 Gms., leukopenia, elevated erythrocyte sedimentation rate, hyperglobulinemia, and positive L.E. cell preparations.

Urinalysis was negative many times. The BUN was 14 mgm/100 ml. and the

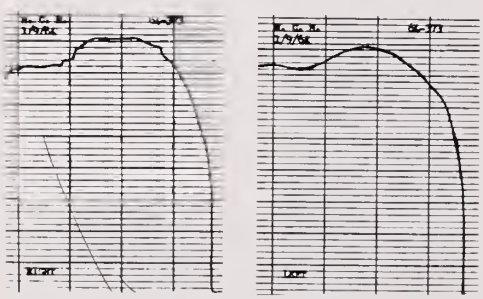


Fig. 2, Case 5: Normal renal function tests, abnormal renogram.

urea clearance 96%. Concentration tests showed a maximum specific gravity of 1.020. The P.S.P. test showed 28% excretion in 15 minutes. The patient was treated with prednisone 60 mgm. daily and after one week, the renographic pattern had returned to normal (Fig. 3).

Group II—Five of the fifteen patients were included in this group. All of them had definite abnormalities in the renal function studies, however, only four were considered to have lupus nephropathy. One patient, Case 7, had pyelonephritis with chills, fever, and pyuria. All of her urinary findings reverted to normal with adequate antibiotic therapy. The radioisotope renogram showed a normal pattern in the left kedney and

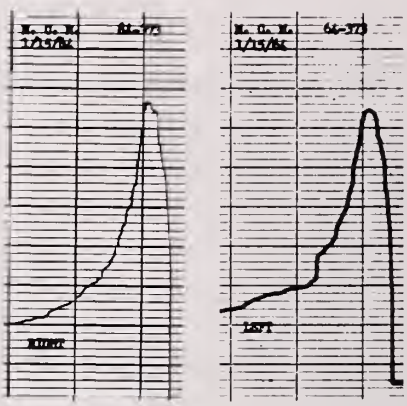


Fig. 3, Case 5: Normal renogram, after one week of prednisone therapy, 60 mgm. daily.

minimal abnormality in the right. The other patient with a normal renographic pattern was Case 10, a 17 year old white girl seen for the first time in February, 1962 with a history of recurrent urticaria, polyarthritis, butterfly rash, fever, weight loss, lymphadenopathy and laboratory evidence of Coombs-positive hemolytic anemia and false positive serological test for syphilis. She had definite evidence of nephritis, with persistent albuminuria, hematuria, pyuria and cylindruria. The L.E. cell preparation was negative but subsequently became positive. She was treated with prednisone 60 mgm. daily for six months and a complete remission was induced. The renographic studies were done in December 1962 when the other renal studies were normal as well as the renographic pattern. She had been well without therapy but recently developed arthralgias and weight loss. Repeated studies revealed only an elevated erythrocyte sedimentation rate, and a positive L.E. cell preparation.

The other three patients in this group

showed markedly abnormal renographic patterns.

Figure 4 shows the abnormal renographic pattern of Case 8, a 21 year old white female who was first seen in 1961 with polyarthritis, fever, anorexia and weight loss of six months duration. Subsequently,

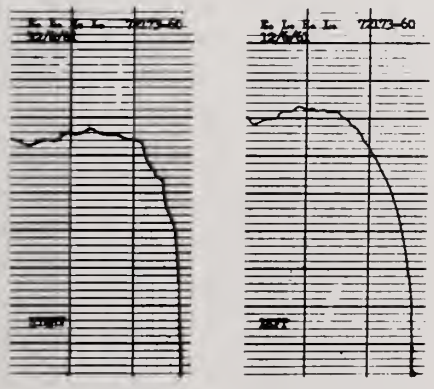


Fig. 4, Case 8: Abnormal renogram, evidence of lupus nephritis by conventional renal function tests.

she developed purpura and anemia and was admitted to the hospital. At that time, she had thrombocytopenia, Coombs positive hemolytic anemia, false positive serological test for syphilis, hyperglobulinemia and positive L.E. cell preparations. Her urinalysis was negative; however, she subsequently developed albuminuria, hematuria, pyuria, cylindruria and the urea clearance decreased. The patient was treated with prednisone, 60 mgm. daily, and in two weeks there was marked improvement in the renographic pattern (Fig. 5). A remission was induced although albuminuria persisted and the urea clearance remained low. In February 1963 she had an exacerbation of her disease and again an abnormal renographic pattern was found (Fig. 6). This reverted toward normal after two weeks on

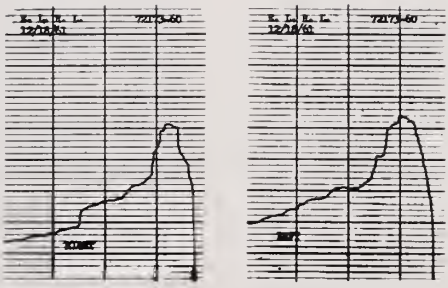


Fig. 5, Case 8: Normal renogram, after two weeks of prednisone therapy, 60 mgm. daily.

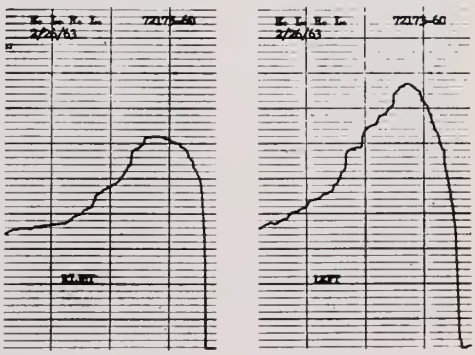


Fig. 6, Case 8: Abnormal renogram, with exacerbation of the disease fourteen months later.

prednisone, 60 mgm. daily (Fig. 7). At present, the renographic pattern and the urinalysis are normal, while the urea clearance is 62%.

Figure 8 shows the abnormal renographic pattern in Case 11. This 27 year old white female was seen in February, 1964 with a one month history of polyarthritis, butterfly rash, purpura, lymphadenopathy

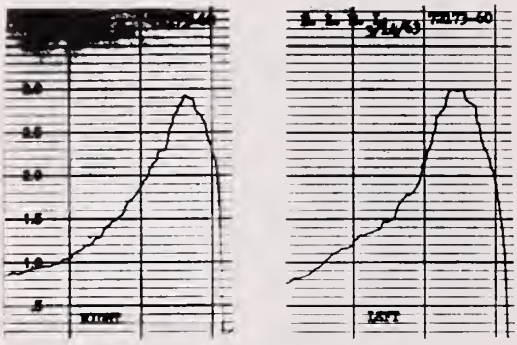


Fig. 7, Case 8: Improvement in the renographic pattern after two weeks of prednisone therapy, 60 mgm. daily.

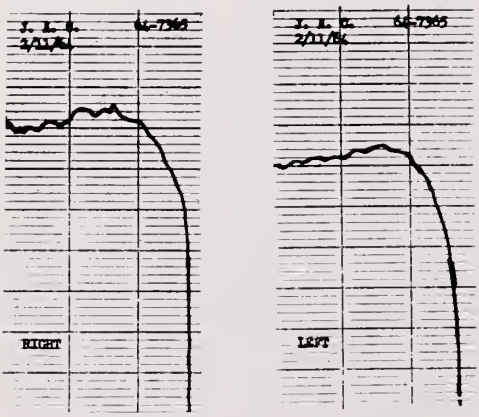


Fig. 8, Case 11: Abnormal renogram with evidence of lupus nephritis in the renal function tests.

and splenomegaly. Laboratory studies revealed a hemoglobin of 7.5 g/100 ml., leukopenia, thrombocytopenia, hypergammaglobulinemia (43%) in plasma protein electrophoresis, positive antinuclear antibody test, and L.E. cell preparations. Renal function studies revealed albuminuria, hematuria, pyuria, cylindruria and mild azotemia. She was treated with prednisone, 60 mgm. daily. This dosage was reduced in two weeks to 30 mgm daily and the renographic pattern, five weeks later, although improved, showed still definite abnormalities (Fig. 9).

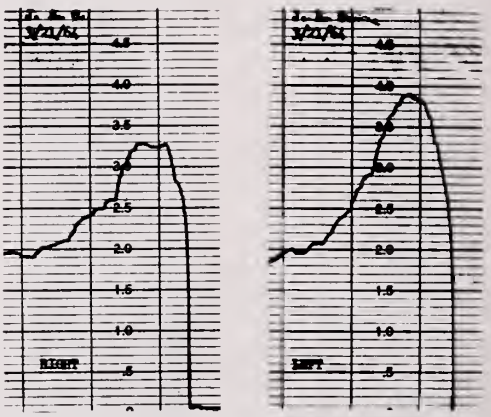


Fig. 9, Case 11: Only some improvement has occurred after inadequate prednisone therapy.

Group III—Four of the fifteen patients were included in this group. They showed severe abnormalities in the renal function studies and the clinical picture of nephrotic syndrome. Table 2 summarizes the clinical features and laboratory findings in this group. Three of the patients were female and their ages ranged from 8 to 62 years. They all had polyarthritis, toxicity and edema. Three had butterfly rash and one had pleuritis. The sedimentation rate was over 30 mm per hour in all, severe anemia was found in three of them, while only two had leukopenia. The L.E. cell preparation was positive in three. In the other patient, the diagnosis was supported by the classical clinical picture, and skin lessions, that upon biopsy showed changes compatible with lupus erythematosus. Two patients had positive latex tests for rheumatoid factor, and one a false positive serology

for syphilis. Hypoalbuminemia was present in all of them, while hyperglobulinemia was found in only two. Serum protein electrophoresis revealed an increase in gamma globulin (over 20%) in three patients and of the alpha 2 globulin in all four. The serum cholesterol was normal in three of them. Massive albuminuria, hematuria, pyuria and cylindruria were present in all patients. All showed some degree of azotemia at some time during the course of the disease, and all had abnormal renographic patterns (Table 3).

Figure 10 shows the abnormal renogram of Case 12, done in early November, 1963. This 21 year old white female had

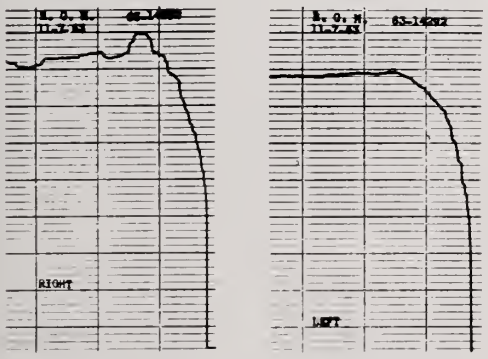


Fig. 10, Case 12: Abnormal renogram in a patient with severe lupus nephritis and the clinical picture of nephrotic syndrome.

polyarthritis for about one year and edema for about three months. She was treated with prednisone, 60 mgm. daily and three weeks later, there had been some improvement in the renographic pattern (Figure 11). By this time, her edema was worse and she was becoming Cushinoid. She was continued on therapy and after six weeks of treatment, her renogram (Fig. 12), was

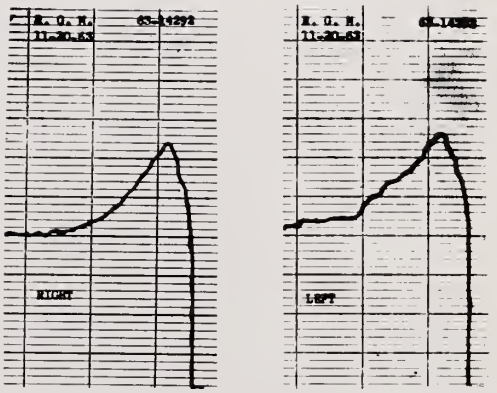


Fig. 11, Case 12: Some improvement has occurred after three weeks of prednisone therapy, 60 mgm. daily.

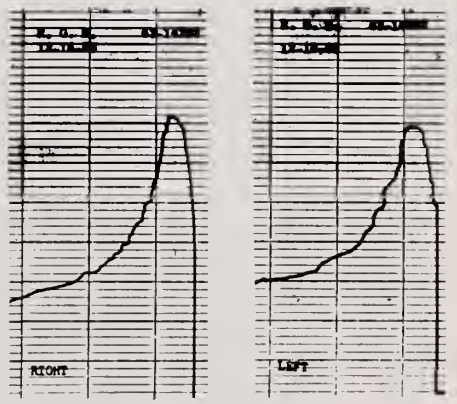


Fig. 12, Case 12: Marked improvement in the renographic pattern has occurred after six weeks of prednisone therapy. Clinically there had been no improvement, the renal function tests were unimproved.

almost normal despite the fact that there had been no improvement in the clinical picture or in the other renal function studies. After almost three months of treatment, the renographic tracing is almost normal (Fig. 13) and she is now clinically improving.

TABLE II: CLINICAL FEATURES, GROUP III

Case No. Sex Age Ys.	Clinical Picture	HB	WBC	ESR	VDRL	R.A.	LE	Cholesterol (mg. %)	T.P.	Serum Proteins Chemical (Gms.%) ALB.	Glob.	Electrophoresis ALB.	Gamma Glob.	Alpha Glob.
12 F 21	Arthritis Butterfly rash Edema Toxicity	11.2	6,000	41	Neg.	Neg.	Pos.	353—451	4.8	2.1	2.7	27.9%	20%	30%
13 F 62	Arthritis Pleuritis Edema Toxicity	7.9	4,000	66	Pos.	Pos.	Pos.	200—240	4.5	2.0	2.5	26 %	33%	17.4%
14 M 8	Arthritis Butterfly rash Edema Toxicity	8.5	8,000	31	Neg.	Pos.	Neg.	124—189	6.1	2.3	3.8	23 %	39%	19%
15 F 25	Arthritis Butterfly rash Edema Cor. pulmonale Toxicity	8.9	2,000	34	Neg.	Neg.	Pos.	126—250	6.6	2.8	3.8	28 %	36%	26%

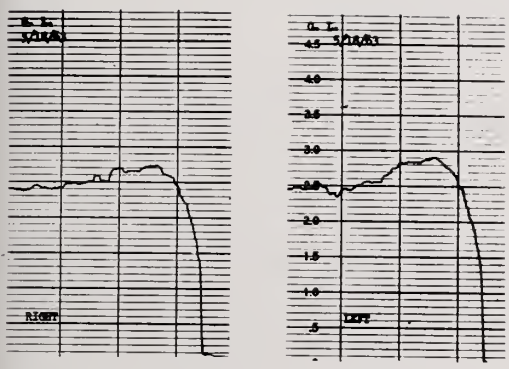


Fig. 13, Case 13: Abnormal renogram in a patient with severe renal involvement and nephrotic syndrome.

Figure 14 shows the abnormal renogram of case 13, a 62 year old white female who was first seen with polyarthritis and pleuritis of one year duration. At this time, a diagnosis of systemic lupus erythematosus was established when the L.E. cell preparation showed many L.E. cells. She was treated with antimalarials and rapidly improved. Six months later she developed the clinical picture of nephrotic syndrome.

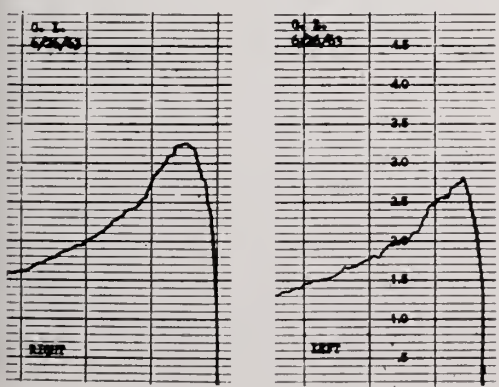


Fig. 14, Case 13: Some improvement has occurred in the renographic pattern after one month of prednisone therapy, 60 mgm. daily.

After five weeks on prednisone, 60 mgm. daily, the renographic pattern showed improvement despite the fact that clinically she was worse and that other renal function studies showed no change. Therapy was continued, and after several months she gradually recovered. After a year she is fairly well except for a residual hemiplegia that subsequently developed.

Case 14, an 8 year old boy, behaved very similar to the above two patients. He developed severe moniliasis and staphylococcal sepsis while under large doses of prednisone. His renal disease, however, improved.

The last case in this group, Case 14 never received adequate corticosteroid therapy, the renographic pattern never improved and she died in uremia shortly after developing the nephrotic syndrome.

Discussion

The incidence of renal involvement in our series of fifty six cases of lupus erythematosus was 68%. In other large series of cases it has been reported to be between 49 and 80% (11). Bunim and Black (12) in reviewing 452 cases reported in the literature found that over half of them had evidence of renal involvement, and in about 25% this was moderate or severe. Prior to the advent of antibiotics, chemotherapeutic agents and corticosteroids, infection and lupus toxicity were the most common causes of death in this disease. Today, the most frequent cause of death is uremia. Persistent albuminuria has been reported to be the most frequent urinary manifestation. In our cases, this was present in 98%, while hematuria was present in 66% and pyuria in 70%. The so-called telescope urine sediment

reported by Krupp (13) characterized by features of acute, sub-acute and chronic glomerulonephritis, is very infrequently observed. Although first thought to be characteristic of lupus nephritis, it has also been observed in polyarteritis, Henoch-Schonlein purpura, and glomerulonephritis. The 15 min. P.S.P. excretion and the creatinine clearance were found to yield the most useful information in terms of appraisal of renal function in the series of cases reported by Soffer, Southern, Weiner, and Wolf (14).

Preliminary analysis of the renographic studies in patients with lupus erythematosus show that the radioisotope renogram is definitely abnormal in all the patients with definite evidence of active lupus nephropathy by conventional renal function studies. The only patient included in this group having a normal study was Case 10. This study was performed after the patient received adequate corticosteroid therapy for six months. Pollack (15) has shown that clinical remission and reversion of the pathologic lesions in the kidney can occur by the use of this dose of corticosteroid for this length of time in patients who are not already in severe renal failure.

Furthermore, of the six patients in Group I, with normal renal function studies, two showed abnormal renographic tracings. Muehrche, Kark, Pirani, and Pollak (1) and Dubois (16) have demonstrated the presence of pathologic lesions in renal biopsies even in patients without clinical evidence of renal involvement. Pollack (15) states that renal biopsies should probably be performed in all patients with systemic lupus erythematosus in order to determine the presence of renal disease. He states: "It is possible that with the detection of an early glomerulitis, steroid therapy may result in cure".

Acute experiments were performed in one patient with abnormal renogram using repeated intravenous injections of hydrocortisone. No effect in the abnormal pattern was detected. Another patient underwent daily renographic study while on 60 mgm. of prednisone daily without showing any improvement in the pattern during the first week. It was noticed that in the patients that clinically had a milder type of renal involvement adequate treatment was followed by return of the pattern to normal in one to three weeks. In these patients when the dosage of prednisone used is lower than 60 mgm. daily, or when the dosage of the drug is reduced below this level prematurely, the renographic pattern although showing some improvement will not revert to normal (Case 11).

This is in accord with previous reports (11) where corticosteroids in low dosages do not alter the natural course of lupus nephritis.

In patients with severe renal involvement and nephrotic syndrome, it took an average of four to six weeks for the renographic pattern to improve. However, renographic improvement was noticed much earlier than clinical improvement, or improvement in the other renal function studies. Only in Case 12, with severe renal involvement and nephrotic syndrome, did the renogram return to normal. In the other two cases, some residual abnormality remained. The fourth patient of Group III who did not receive adequate prednisone therapy the renographic pattern remained unchanged and she died in uremia several months after the onset of the nephrotic syndrome.

TABLE III: RENOGRAPHIC STUDIES RESPONSE TO TREATMENT (GROUP III)

		Renal Studies						
Case No.	Date	Alb	RBC	WBC	Cast	BUN	Prednisone	Renogram
12	10/25/63	4 +	4 +	4 +	4 +	13	60 mgm	Abnormal
	11/20/63	4 +	4 +	4 +	4 +	21	" "	Improved
	12/16/63	3 +	1 +	1 +	1 +	16	" "	Normal
	2/18/64	1 +	0	0	0	14	" "	Normal
13	11/16/62	±	0	0	±			
	5/18/63	3 +	3 +	+	3 +	22	60 mgm	Abnormal
	6/26/63	3 +	3 +	+	2 +	31	" "	Improved
	7/12/63	3 +	3 +	0	2 +	25	" "	
14	7/30/62	0	0	0	0		20 mgm	
	8/22/63	2 +	3 +	±	2 +	14	60 "	Abnormal
	9/20/63	2 +	4 +	1 +	2 +	25	" "	Improved
	11/11/63	1 +	1 +	±	+	15	" "	Improved
15	3/31/58	1 +	0	4 +	0			
		2 +	1 +	1 +	1 +	23	30 mgm	Abnormal
		2 +	1 +	1 +	1 +	88	" "	Abnormal

These findings demonstrate that the radioisotope renogram is abnormal in all untreated patients of lupus erythematosus with renal involvement even when no abnormalities are detected by the usual renal function tests. Furthermore, response to therapy is evidenced earlier in these tracings. Apparently, the time necessary for the renographic tracing to improve is directly proportional to the severity of the renal involvement when the patient is receiving adequate corticosteroid therapy. Progression of the disease is accompanied by failure of the renographic tracing to improve.

Summary

Renographic studies were performed in fifteen patients taken from a series of fifty six cases of lupus erythematosus. Nine of the patients studied had evidence of renal disease and in eight, this was considered to be lupus nephritis. Of these, seven had abnormal renographic tracings, in the other, the study was performed after the disease was in remission. Two of the six patients with no evidence of renal involvement by the conventional renal function studies also showed abnormal renographic patterns.

In those patients with only renographic evidence of renal involvement (Group I) and those with definite evidence of lupus nephritis in conventional renal function studies but only mild to moderate clinical nephritis (Group II), the renographic pattern reverted to normal one to three weeks after the institution of adequate corticosteroid therapy. In one of them, the dosage of corticosteroid was prematurely reduced and the tracing showed improvement only after five weeks of therapy.

In the group of patients with severe abnormalities in the conventional renal function studies and the clinical picture of nephrotic syndrome, Group III, the renographic pattern showed improvement only after four to six weeks of therapy. In only one of the patients in this group did the renographic tracing return to normal. Another patient did not receive adequate corticosteroid therapy and she died in uremia several months after the onset of the nephrotic syndrome without showing at any time improvement in the renographic pattern.

In all the patients studied there was improvement in the renographic pattern much earlier than in the clinical picture and the other renal function studies.

Although the number of patients studied is too small, and the observations limited, it appears that the radioisotope renogram may detect renal involvement in lupus erythematosus much earlier and with greater frequency than the conventional renal functions studies. Furthermore, the rapidity with which the renogram reverts to normal with adequate corticosteroid therapy is an index of the severity of the renal disease and has prognostic implications.

Resumen

De un total de 56 casos de lupus eritematosus se estudiaron 15 usando el renograma radioactivo. En 9 de ellos se encontró evidencia de enfermedad renal, en 8 de los cuales se consideró que esta se debía a una nefropatía. En 7 de los mismos el trazado fue anormal, habiéndose hecho el estudio en el otro caso después de que la enfermedad había remitido. En 2 de los 6 casos donde no se encontró evidencia de afec-

ción renal con el uso de las pruebas de función renal, el estudio renográfico fue anormal.

En aquellos pacientes en quienes tan sólo se encontró evidencia renográfica de afección renal (Grupo 1), y en aquellos en los cuales las pruebas de función renal evidenciaban nefritis, pero en los que clínicamente la enfermedad renal no era severa (Grupo 2), el patrón renográfico regresó a la normalidad después de una a tres semanas de terapia con corticosteroides en dosis adecuadas. En uno de éstos, a quien se le redujo la dosis prematuramente, el trazado reveló tan solo mejoría después de 5 semanas de tratamiento.

En el grupo de pacientes con anormalidades acentuadas en las pruebas de función renal y que mostraban el cuadro clínico del síndrome nefrótico (Grupo 3), el patrón renográfico demostró mejoría después de 4 a 6 semanas de terapia adecuada. En solamente uno de los pacientes de este grupo regresó el patrón renográfico a la normalidad. Otro de los pacientes de este grupo no recibió terapia de corticosteroides a dosis adecuadas y murió en uremia varios meses después de desarrollar el síndrome nefróti. co. El trazado renográfico de esta paciente nunca mejoró.

En todos los pacientes estudiados el patrón renográfico mejoró mucho antes de que se observara cambio alguno en el cuadro clínico. Las pruebas usuales de función renal también permanecían anormales por un período largo de tiempo.

Aunque el número de pacientes estudiado es reducido y las observaciones limitadas, se obtuvo la impresión de que el estudio renográfico tiende a describir afección renal en los pacientes con lupus eritematosus mucho antes y con mayor frecuencia que otras pruebas de función renal. Además, la rapidez con que el trazado renográfico regresa a la normalidad cuando el paciente recibe dosis adecuadas de corticosteroides es un índice de la severidad de afección y tiene significación pronóstica.

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A REVIEW

PYELONEPHRITIS IN THE DIABETIC

Agustín M. de Andino, M.D.

With the increased life span of the diabetic patient and his apparent ability for contracting infections readily, the study of the kidney and of the infections which affect the entire urinary tract assumes increasing importance. The physician must be aware of those conditions to which the diabetic is vulnerable so that he may treat them early and avoid irreparable damage that may either kill him or shorten his life.

The greatest problem which the diabetic patient faces today is that of vascular disease. Nevertneless, when one analyzes the causes of death in diabetics, one still finds an appalling number of complications which bear no relation to vascular degenerative disease. It is thus imperative to pay continuous and exacting attention to all details in the management of the diabetic state, and specially to those conditions associated with infection.

The renal lesions which are associated with diabetes mellitus are as follows:

1) Reversible metabolic phenomena.
   a) Glycogen deposits in the tubules.
   b) Fat deposits in the tubules.
2) Arteriolar sclerosis.
3) Intercapillary glomerulosclerosis — nodular and diffuse.
4) Acute and chronic pyelonephritis — to include necrotizing renal papillitis.

It is well to emphasize that as a rule it is common for two or more lesions to be found together in the same kidney. This is particularly true of the last three conditions enumerated, that is, a combination of extra and intercapillary vascular disease, and of acute and chronic infection. When this occurs, as it happens in the diabetic of many years, and specially in the juvenile one with his early onset of disease, the kidney shows a mixture of renal lesions spoken of as "mixed diabetic nephropathy".

The importance of urinary tract infection in cases of diabetes has been emphasized mostly in studies of autopsy cases. The statistics at the Joslin Clinic (1) show that in 422 autopsies performed from 1919 to 1945 infection of the genitourinary tract was found in 20% of the cases. In 100 cases at the same clinic autopsied between 1945 and 1950, 30% showed evidence of urinary tract infection. Robbins and Tuckner (2) in 1944 in their series of 307 diabetic deaths found that pyelonephritis was the sixth cause of demise, being responsible for 21 of the fatalities. They found evidence of acute pyelonephritis in 1 out of every 5 autopsies in diabetic patients. The marked in-

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fluence of antibiotic therapy on mortality from renal infection is clearly established in a recent publication by Warren (3). In this paper he reviews the causes of death among 1358 diabetic patients observed at the Joslin Clinic between 1950 and 1953. The main cause of death in this large series was vascular sclerosis (cardioreno-cerebrovascular disease) which accounted for 71.6% of the fatalities, divided as follows: 47.1% dying of cardiovascular disease, 12.2% of cerebrovascular disease, and 12.3% of renovascular disease. More than 90% of the renal deaths were classified as mixed diabetic nephropathy, indicating that infection played an important part in this type of death. Acute kidney infections accounted for only 5 cases out of the whole series of 1358 cases, yielding only 0.4% of the total.

It is of interest to review some of the aspects of experimental pyelonephritis, and specially in relation to the diabetic animal. Initial attempts by Schofield and Baker (4), working mostly with mice with alloxan diabetes, failed to demonstrate an increased susceptibility of this animal to renal infection except in the early toxic stages of the alloxan effect. In 1963 Boshell and his collaborators (5), working with chronically alloxanized diabetic rats, proved that there exists an increased susceptibility of these animals to pyelonephritis. Of the diabetic rats 76.3% showed evidence of active tissue infection (more than 100,000 organisms per m l of Kidney tissue solution) while the non-diabetic rats showed only 10% infection when they were inoculated intravesically with *E. coli*. An intravesical inoculum of *Proteus vulgaris* produced 98% infection in diabetic rats and 47% in the nondiabetic controls, clearly demonstrating the increased virulence of this organism.

Another interesting part of their experiment consisted of the comparison of the effects of an intravenous inoculum of *E, coli* in diabetic and nondiabetic rats. None of the alloxan diabetic rats and just one of the alloxanized nondiabetic rats had evidence of active infection by the tissue count method. This contrasted dramatically with the effects seen when the intravesical route was used.

To determine if glycosuria per se played an important role in the development of experimental kidney infection the susceptibility of phloridzinized rats with active glycosuria to the intravesical inoculation of *E. coli* was studied. There was no difference in the degree of infection per ml of kidney tissue solution in the treated animals when compared with the nonphloridzinized controls. The results tend to indicate that glycosuria per se does not enhance the susceptibility of rats to experimental kidney infection.

The inflammatory changes in the affected animals generally consisted of small foci of interstitial fibrosis with round cell infiltration located beneath the parietal epithelium of the calyx and scattered throughout the cortex in the milder lesions. The more advanced and destructive lesions showed large areas of interstitial fibrosis, obliteration of tubules, inflammatory cell casts, small foci of hemorrhage, and diffuse infiltration by both polymorphonuclear and mononuclear inflammatory cells. Large abscesses and punched-out areas were observed grossly in the more severely infected kidneys.

The majority of the kidneys in the alloxanized diabetic rats showed some degree of vacuolization of the tubular cells of the loop of Henle and distal tubules. With colloidal iron — PAS preparation they showed

marked deposits of glycogen. These changes are quite different from those seen in the kaliopenic nephropathy where there is marked hydropic degeneration of the tubular cells without the presence of glycogen. These changes are similar to those described by other investigators in rabbits and rats made diabetic with alloxan. The pathological evidence of infection confirmed the tissue bacterial counts in that there was a distinct correlation between the incidence of plus 3 and plus 4 pathological changes in the animals with bacterial counts over 10,000 colonies per ml of kidney tissue as compared with the association of plus 1 and plus 2 pathological changes in the animals with bacterial counts below 10,000.

An outstanding feature of the experiments using *Proteus vulgaris* was the remarkable tendency of this organism to produce the most severe lesions, characterized pathologically by necrosis and sloughing of the tip and/or the side of the pyramid.

Recently, the widely accepted fact of the prevalence of renal infection in the diabetic has been challenged by a series of stimulating articles from widely separated areas of the world. These studies have been prompted by the wire discrepancy which exists between the frequency of pyelonephritis in necropsy material an its prevalence in living patients. This fact and the revival of quantitative bacterial counts by serial dilution or urine specimens has lead to a new interest in the subject, specially when the bacterial count method has provided a tool to differentiate between true bacteriuria and contamination. The first of this series of articles appeared in 1959 under the authorship of Huvos and Rocha (6) from the Grace — New Haven Hospital. They studied fifty diabetic patients and fifty nondiabetic controls paired as to the age and sex. The urine specimens were taken by the clean — catch, mid — stream method, and cultures of the diluted urine (1:100) were prepared inmediately. There was no difference in the incidence of positive cultures in either group (26% and 22% respectively). The incidence of positive cultures was significantly higher in the elderly patients (30%) as compared with the young patients (4%). No difference was observed in the incidence of bacteriuria between the sexes, even in the elderly group. This might have been due to the smallness of the series, as this finding is at variant with all the other series reported in which the incidence of positive urine cultures is significantly higher in the elderly female, both diabetic and nondiabetic. They also reported a high incidence of significant bacteriuria in patients with a previous history of genital manipulation and/or catheterization. In their communication the authors emphasized the presence of factors such as acute or chronic illness, poor nutritional status, age, general debility, and previous manipulation of the genital tract as being more important in relation to the urinary infection than the presence or abscence of diabetes.

The second of these challenging papers was authored by Szucs and his colleagues (7) from one of the large charity hospitals in Budapest, Hungary. These individuals, using the bacterial counts of diluted urine as the diagnostic tool, studied 300 ambulatory diabetic patients and 300 controls paired as to age and sex. Both groups were from their outpatient department. They found significant bacteriuria in 6% of the diabetic patients, the same incidence as in the control group. The only difference between the two groups was that the bacterial counts in

the urine of the diabetic patients were higher than in the controls. Both the female diabetic patients and the female controls exhibited higher bacterial counts than their male counterparts. If the curve of bacterial counts of the well controlled diabetic patients and that of the controls was compared, no difference was observed, while if the curve of the poorly controlled patients was compared with that of the controls, there was a significant difference present. No difference was observed between diabetics controlled with carbutamide, with diet alone, or with diet plus insulin. On the basis of their published data Szucs and his collaborators concluded that the old concept of increased frequency of pyelonephritis in diabetic patients has to be revised and reinvestigated in terms of other factors which alter the epidemiological approach to this question.

The third group of doubting Thomases hails from England and their views are expounded in an article published in the March 18, 1961 issue of the British Medical Journal. O'Sullivan and his coworkers (8) used the same methods quoted before in their analysis of 150 asymptomatic patients from the general diabetic clinic as compared to a paired group of asymptomatic controls. Both of these groups corresponded in age and sex with the general clinic population. In both groups there was a preponderance of middle – aged and elderly women, and in both groups the largest number of patients was found in the age group above forty years. No difference was observed in significant bacteriuria (above 100,000 colonies per m l of urine) between the diabetic and nondiabetic group (13.3% vs. 12.0%). If the incidence of infection was compared between the sexes there was a striking difference between the male and the female. Among the 20 infected diabetics, 18 were found to be women; in the control group, among the 18 infected patients, 17 were found to be women. In this communication, the same as in the previous one, the one important difference between the diabetics an the controls was found in the height of the bacterial counts among those infected. Most of the infected diabetics had counts above 1,000,000 colonies per m l, while only 7 of the 18 infected controls had counts as high as this. The authors believe that the presence of heavy glycosuria was a favourable medium for the more rapid multiplication of the organisms. The authors concluded that there is no doubt in their mind that urinary infections are no more common among diabetics than among nondiabetics. They state that "clinical impressions have always suggested an increased incidence of urinary tract infection among diabetics, but since both diabetes and urinary infections occur most commonly in elderly and middle – aged women, it is not surprising that the number of diabetics with infection would seem to be so high". They recomend the continuation of studies on this problem, and specially the search for asymptomatic urinary tract infections in the general healthy population by the quantitative studies of the clean urine specimen.

It is of interest to both the internist and the urologist to note that the question of the mode of spread of infection into the urinary tract has been lately the subject of much discussion. As I pointed out at the beginning of this talk Boshell and his coworkers (5) were unable to detect any unusual predisposition to kidney infection in either the diabetic or the nondiabetic rat

when both groups were given large intravenous inocula of *Eschericia coli*. On the clinical side Joron and his colleagues (9) from the Montreal General Hospital in a bacterial study of bladder urine done in 409 diabetic patients and in 280 controls found that pyelonephritis in the asymptomatic diabetic or control is present or likely to develop if the same organism is recovered repeatedly from the cultured urine, and specially if there is associated pyuria. Dr. Howard Root from the Joslin Clinic (10), in a discussion which followed Joron's (9) presentation, commented that in their series of cases there was a marked predominance of the colon bacillus in the female patients as compared to the male ones. It seemed reasonable for him to infer that the predominance of *E. coli* in the female was indicative of urethral contamination since blood-borne infection would occur with equal frequency in both sexes. In his series of cases Root (10) found that the route of infection was of the retrograde type in 64 cases (84%). Of these 64 cases he found instances (78%) of complicating lesions that lead to infection, among which were included urethral stenosis, urethral polyps, polyps of the bladder, bladder diverticula, bladder stones, bladder carcinoma and renal stones. In many of these cases there was a history of instrumentation, as a rule of the use of a urethral catheter. There were only 12 cases (16%) in which the route of infection was found to be hematogenous. It must be emphasized that these patients were examples of recalcitrant urinary infections who had been referred to the Joslin Clinic because of poor response to therapy.

My review would not be complete without saying a few words about one of the most dreaded complications of pyelonephritis in the diabetic, the syndrome of necrotizing renal papillary necrosis. It was described by von Friederich (11) in 1877 in a 70 years old man with an obstructive uropathy. In 1937 Froboese (12) and Gunther (13) first emphasized its frequent association with diabetes mellitus. In 1952 Mandel (14) reviewed the available literature which included 160 cases. He urged that the diagnosis be suspected *in vivo* in patients with diabetes and urinary obstruction in whom there occurs rapid and progressive renal insufficiency combined with urinary and systematic bacterial infection. In 1958 Hashim (15) reviewed the world's literature and was able to find 203 cases, predominantly in patients over the age of fifty years. The overwhelming majority of the cases had been diagnosed at postmorten examination. Among the 183 cases which he was able to tabulate, 115 occurred in diabetics (62.8%). Of the remaining 68 nondiabetics (37.2% of the series), 49 occurred in patients with obstructive uropathy. Only 19 of the cases (10.3% of the total) were found to be free of either diabetes or urinary obstruction. Two thirds of the diabetic cases occurred in women, whereas among nondiabetics the men outnumbered the women six to one. The majority of the cases in both groups were found to be above the age of fifty and the lesion was unilateral in one third of the cases.

The pathogenesis of necrotizing renal papillitis remains obscure. Pathologically it resembles an ischemic necrosis of the renal papilla with concomitant bacterial infection. It might be present in a subacute fashion, characterized by a pyelonephritis of several weeks or months' duration with acute exacerbations, or as an acute fulmi-

nating disease characterized by overwhelming sepsis and circulatory collapse.

The necrosis has never been reported to involve the renal cortex. Experimental studies by Mandel and Popper (16) on vinylamine – induced medullary necrosis emphasize the importance of vascular injury and thrombosis as important etiologic factors in the abscence of diabetes or urinary obstruction. Vascular congestion in the renal medulla, as would result from severe infection, may be equivalent to complete cessation of blood flow with resultant ischemic necrosis if the stasis is of sufficient duration. Upper urinary infection, which is of the ascending type in the majority of the cases where human medullary necrosis has been reported, may predispose to the development of renal medullary vascular disturbance. The mere existence of a chronic latent pyelonephritis might make the diabetic patient more likely to develop necrotizing papillitis than if it were nonexistent. Some authors like Edmonson (17) and Eskelund (18) have implied a definite relation between this condition and intercapillary glomerulosclerosis, but others have interpreted this as a chance occurrence. Further studies in the pathogenesis of this interesting condition are needed.

Summary

I have presented a short review of the recent clinical and experimental work on pyelonephritis as it pertains to the diabetic patient.

Boshell and his coworkers (5) have proved that there exists an increased susceptibility of the diabetic rat to experimental pyelonephritis by the inravesical route, but not by the intravenous one.

The widely accepted idea of the prevalence of renal infection in the diabetic has been challenged by well controlled studies in Hungary (7), Great Britain (8), and the United States (6).

Acute necrotizing papillitis or renal papillary necrosis, although infrequently reported, appears to be more common than is supposed. More clinical and experimental studies are needed to elucidate the pathogenesis of this condition.

Resumen

He presentado una revisión corta y concisa de los trabajos experimentales y clínicos de publicación más reciente sobre la pielonefritis crónica en el paciente diabético.

El trabajo experimental de Bashell y sus colaboradores prueba de una manera conclusiva que existe un aumento en la susceptibilidad del ratón diabético a la pielonefritis provocada por la inoculación intravesical de bacterias, pero no así a la pielonefritis por inoculación intravenosa.

Se cuestiona seriamente por investigadores en Estados Unidos, la Gran Bretaña y Hungría el hecho mundialmente aceptado que el diabético es más susceptible a las infecciones del tracto urinario que el no diabético.

Aparentemente la papilitis necrotizante aguda es una complicación más frecuente de lo que se desprende de los informes en la literatura médica. Necesitamos más estudios clínicos y experimentales para poder entender mejor los mecanismos patofisiológicos afectados en esta condición de pronóstico tan serio.

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CASE REPORT

INCLUSION BODY ENCEPHALITIS IN A PUERTO RICAN CHILD

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Subacute inclusion body encephalitis (SIBE) was first described in 1933 by Dawson (1) who reported two cases from Tennessee and first used the name. The disease was characterized by diffuse cerebral degeneration and the presence of intranuclear inclusion bodies. In 1945 Van Bogaert (2) described a disease with a similar clinical picture under the name of subacute sclerosing leuco-encephalitis. Intranuclear inclusion bodies were later demonstrated in this disease and the two are now considered to be the same entity.

Up to October, 1962 forty-three cases had been reported in the English literature (3) and since then, several more have been reported from English and European countries. Seventy-nine cases were reported from Belgium where the disease is considered to be endemic by the authors (4). Fourteen cases were reported from Canada (5), five cases from Scotland (6) and three cases from Czechoslovakia (7). The present case represents the first such report from Puerto Rico and, to our knowledge, the first case reported in a Puerto Rican. Because of the presence of intranuclear inclusions, a viral etiology is suspected. Others have suggested an immune mechanism (7) and two instances of the disease occurring in families have been reported (6) although a genetic mechanism is not suspected.

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Presented at the First Annual Meeting of the Puerto Rico Academy of Neurology, San Juan, P. R. June 1965.

Case Report

A 10 year old boy, was apparently well until two weeks prior to admission when he developed abnormal gait, tremors in the upper extremities, and intermittent colicky diffuse abdominal pain of a few minutes duration. Within a week, sphincter incontinence occurred. On April 6, 1964 he became lethargic and was admitted to the San Juan City Hospital.

Past history revealed an apparently normal birth and early growth and development. At four months of age, the patient had a previous admission to San Juan City Hospital with gastroenteritis, ear discharge, cyanosis and convulsions. This condition apparently subsided with treatment. There was history of mumps and measles at age four and five years respectively, without apparent sequelae. A history of poor school performance was obtained. He had failed the first grade of school and had performed poorly in the second. In the third grade, at time of admission, he had been noted to be forgetting how to do simple arithmetic problems previously easy for him. Five months prior to admission he was affected by a dengue-like sympton complex at the time of an epidemic of the disease. This subsided without apparent complications.

Family history revealed diabetes and hypertension in the mother, an obese female sibling with seizures

and poor grades in school, and an obese male sibling with poor school grades. A third male sibling was apparently healthy with normal school performance. There was history of tuberculosis in a distant relative but no significant history of contact with the patient.

Blood pressure was 110/70, mm Hg., pulse 104 per minute, respirations 24/min., temperature 100°F, weight 109 lbs. (above 97 percentile), height 57" (at 75 percentile). The patient was a well developed, obese, chronically ill appearing male child, with a sad, frightened facies; there was no spontaneous speech. He lay in bed on one side drooling saliva. Intermittent automatic lip smacking movements were noted, and a feeble whimpering sound occurred intermittently. Rhythmic tremor of the left arm and hand was noted, and the arm was held flexed across the chest. He reacted to command with spontaneous crying, but was unable to respond otherwise.

The head was normocephalic and the neck was not stiff. Cranial nerves examination revealed no abnormalities. The patient was unable to respond for muscle testing but cog-wheel rigidity was present in both upper extremities. Cerebellar function could not be evaluated adequately. The deep tendon reflexes were normoactive and symmetrical. Both plantar responses were flexor. Response to painful stimuli was noted in all extremities but finer sensory testing was not possible. The general physical examination was not remarkable.

Differential diagnosis at the time of admission included a diffuse encephalitis, diffuse cerebral degeneration, one of the lipoidoses or one of the leukoencephalopathies. The significance of the family history was not apparent.

X-rays of the skull were normal. Lumbar puncture revealed clear cerebrospinal fluid with no cells, Sugar, 72mg.; protein, 46.4mg., chloride, 117mEq/L. White blood cells, 9,100 cu.mm., hemoglobin, 11.5 g; neutrophiles, 70%, lymphocytes, 28%, eosinophiles, 2%. Urine was yellow, cloudy, alkaline in reaction with specific gravity of 1.012. Albumin and sugar were negative. Many bacteria and triple phosphate crystals were seen.

Electroencephalogram was reported as follows: Abnormal record. Paroxysmal epileptiform activity alternated with periods of relative low voltage suggesting a subcortical origin as described in various forms of subacute encephalitis.

Twelve days after admission, lumbar puncture was repeated and again the fluid was clear with no cells. Protein was 49.1 mg and sugar 77 mg. Traces of globulin were detected by the Pandy reaction and the chloride was 116 mEq/L. Colloidal gold cure was 5,5,5,3,2,0,0,0,0,0. VDRL was negative. On the eighteenth hospital day pneumoencephalography was performed which was normal. On the twentieth hospital day leukocyte count was 14,850/cu. mm. and the hemoglobin was 12.2 g. Throat culture grew yeast and aerobic gram negative bacilli. Electroencephalogram again revealed a diffusely abnormal tracing without specific pattern. On the twentysixth hospital day leukocyte count was 10,000/cu. mm. Blood culture produced no growth. On the twenty-ninth hospital day lumbar puncture yielded clear fluid with 4 mononuclear cells; sugar, 77 mg; protein, 70.4 mg; chloride, 123 mEq/L and negative VDRL. Serum VDRL was also negative PPD (intermediate strength) was negative.

Erythrocyte sedimentation rate was 26 mm in one hour.

Because of the tremors and rigidity, Benadryl ® and Artane ® were given originally without apparent effect. Later diphenylhydantoin and phenobarbital were begun because of automatic movements and these were partially controlled. Fluctuating fever gradually developed, and with progressive deterioration, swallowing became impossible, necessitating tube feeding. Because of the electroencephalographic pattern, a tentative diagnosis of S.I.B.E. was made. Therapy with prednisone 60mg. daily and oxytetracycline 1g daily was instituted. Minimal improvement was noted on this regimen. Within three weeks a complicating bronchopneumonia developed and the patient expired two weeks later.

No gross changes were apparent externally or on section of the fixed brain.

Microscopically there was slight loss of cortical neurons with slight reactive astrocytosis. Scattered and few Type A intranuclear inclusion bodies were found in neurons, astrocytes and oligodendroglia. There was diffuse lymphocytic perivascular cuffing. In the white matter there was pallor, rarefaction and moderate to marked astrocytosis. These areas were patchy and scattered and revealed loss of myelin and axones with special stains. (Figs. 1, 2, 3, 4).

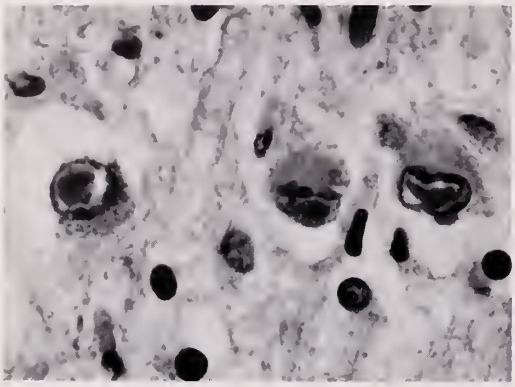


Figure 1: Type A intranuclear inclusion bodies in neurons.

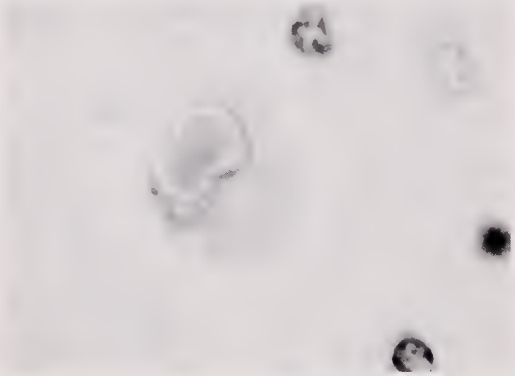


Figure 2: Well demarcated intranuclear inclusion body in neuron under higher magnification.

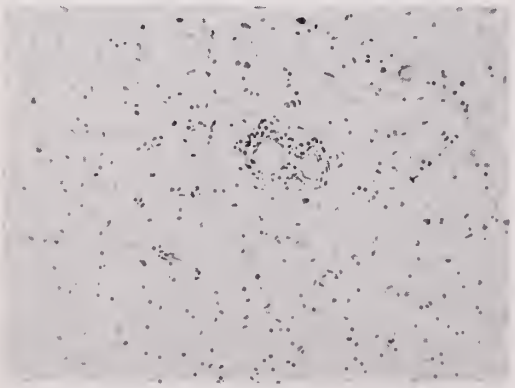


Figure 3: Lymphocytic perivascular cuffing and astrocytic gliosis in white matter.

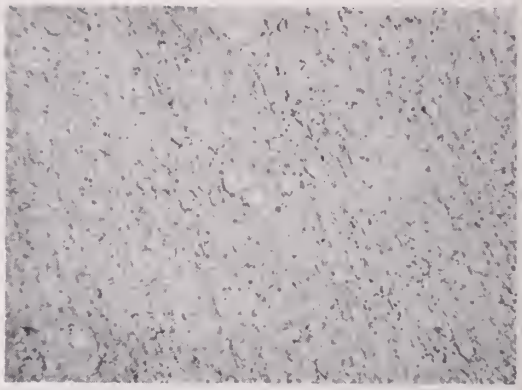


Figure 4: Rarefaction, astrocytosis and loss of myelin in white matter.

The same histological picture prevailed throughout all the sections taken. However, in the hippocampus the changes were more marked and glial shrubs were present. In the pontine section, the intranuclear inclusion bodies were more abundant and the neuronal loss more marked.

Discussion

The presenting picture, clinical course, laboratory data, and pathological findings of this case are characteristic of SIBE. The EEG changes are striking when present and in the present case, combined with the first zone colloidal gold curve and clinical picture, enabled the diagnosis to be made during life.

The experience recorded in the literature reveals ages of onset usually ranging from 4 to 22 years. Males are affected more frequently than females, 3: 1. (4). Early clinical manifestations include insidious progressive intellectual deterioration associated with incontinence, myoclonic jerking, extrapyramidal movements, rigidity, characteristic facial expressions and occasional seizures. A "paretic" or first zone colloidal gold curve is frequently found in the CSF in

the presence of negative serological tests for syphilis. The protein may be slightly elevated but the fluid is usually otherwise normal.

A characteristic EEG pattern was reported in Van Bogaert's subacute sclerosing leukoencephalitis by Radermecker in 1949 (8) and later by Cobb and Hill in 1950 (9) in inclusion body encephalitis of Dawson. A previous report by Balthazar in 1944 (10) was noted by Radermecker (11) in a case of nodular panencephalitis of Pette-Doring. The three are generally considered to be the same by contemporary authors and the pattern has become associated with subacute encephalitis.

Since that time, multiple case reports have borne out the relative specificity of the EEG pattern and it is considered diagnostic by some authors (8, 12, 13). Against a background of low voltage irregular activity, paroxysms of higher voltage slow or sharp discharges occur, at times with striking regularity (Fig. 5). The pattern may be present at various stages of the disease and absent at other times in the same patient. The bursts are usually associated with minor or major myoclonic movements, although the pattern tends to persist in sleep when the patient is motionless.

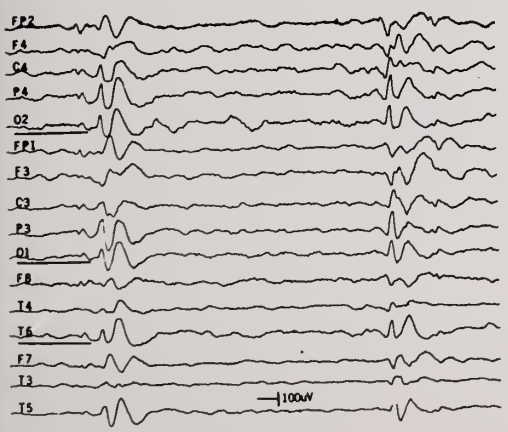


Figure 5: Electroencephalogram showing characteristic pattern of periodic paraxysmal higher voltage slowing against relatively lower amplitude background activity.

No genetic pattern has been demonstrated in the disease and cases usually have been sporadic. Although herpes simplex has been demonstrated in cases with similar inclusion bodies (14) and some cases recently reported had history of viral hepatitis (15) proof of a viral etiology is yet forthcoming. No therapy has been reported to be succesful and the disease has been usually fatal.

The importance of finding the disease in this country, in a Puerto Rican never outside of Puerto Rico, lies in the epidemiologic possibilities in an apparently nonfamilial disease of suspected viral etiology.

Summary

A case of subacute inclusion body encephalitis is reported in a Puerto Rican male child with autopsy demonstration of classical features. The disease is discussed and the literature briefly reviewed. The combination of classical clinical features and a characteristic EEG pattern, considered to be strongly suggestive of the disease, enabled the diagnosis to be made prior to death.

Resumen

Se presenta un caso de encefalitis subaguda por cuerpos de inclusión en un niño puertorriqueño con cuadro sintomatológico y hallazgos de laboratorio y patológicos característicos. El diagnóstico clínico se establece por síntomas y signos de degenera-

ción cerebral difusa coincidiendo con un patrón electroencefalográfico considerado específico y un líquido encefalorraquídeo normal excepto por una curva de oro coloidal de tipo parético. La etiología de esta condición se desconoce, y no se ha descrito tratamiento adecuado alguno. El pronóstico es generalmente fatal. Los hallazgos microscópicos en la corteza cerebral son pérdida de neuronas con astrocitosis reactiva y la presencia de cuerpos de inclusión intranucleares en neuronas y glía. Hay también infiltrados linfocíticos perivasculares. En la materia blanca hay áreas de rarefacción, astrocitosis y pérdida de mielina.

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CASE REPORT

HEMOLYTIC DISEASE OF THE NEWBORN DUE TO UNUSUAL ANTIBODIES

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In 1939 Levine (1) suggested a theory for the pathogenesis of hemolytic disease of the newborn. It proposed that the fetus inherits a blood factor from the father which is absent from the mother's blood and stimulates the production of antibodies in the mother which pass through the placenta and destroy the fetal red blood cells.

Erythroblastosis is most commonly found among Rh_0 (D) positive children born of Rh_0 (D) negative mother but an incompatibility of other blood factors between the fetus and mother may lead to the same pathological process. It should always be remembered that Rh positive women, though rarely, may produce erythroblastotic children as a result of immunization to various blood factors (2). It is our purpose to describe a case of severe hemolytic disease of the newborn occurring in the infant of an Rh_0 (D) positive mother due to immunization to the S factor.

Case Report

Baby girl was born of a normal delivery at the San Jorge Hospital on June 6, 1966 at 4:19 p.m. She weighed 6 lbs. The newborn was covered with thick yellow meconium. She required active resuscitation but recovered promptly. Soon after birth the conjunctivae and umbilical cord were observed to be jaundiced.

The mother's pregnancy was uncomplicated except for excessive weight gain of 30 lbs. There had been no neo-natal problems with the other five children who are living and well except one who has a congenital heart condition.

Both mother and baby were group 0, Rh_0 (D) positive. The direct Coombs test was 3 plus, some antihuman sera giving weakly positive reactions. Complete rh typing is shown in Table I.

The mother was found to be S negative and baby S positive. Identification of the atypical antibody in the mother's serum utilizing identigen panel cells* pointed towards anti-S as the cause of the hemolytic disease (Table II). Results of serial bilirubin determinations and of hemoglobin values are found in Table III.

On June 7 urine bilirubin was strongly positive. The hemoglobin was 5%; hematocrit, 16%; erythroblasts, 64,000/cu. mm; reticulocytes 70%. Four exchange transfusions with compatible blood were performed and a 60 ml blood transfusion was given to the infant. In view of the very high direct bilirubin values a hepatic condition probably related to the presence of bile plugs was suspected and the infant was given hydrocortisone intramuscularly, 6 mg, every 8 hours, for 5 days. The bilirubin was 5.4 mg the hemoglobin was 11.3 g on June 15. The baby was discharged in good condition on June 16.

Discussion

In 1927 Landsteiner and Levine (3) discovered the M and N agglutinogens.

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* *Supplied by the Blood Bank of the Puerto Rico Medical Center.*

Either one or both factors must occur in every individual. Discovery of a new antibody, anti-S, in 1947 (4) disclosed a new blood agglutinogen associated with the MN system. Anti-s was described by Levine et al (5). S and s are alleles but not allelic to M and N. A third allele U called Su has recently been proposed (6). Anti-U sera react as anti-Ss and have been found associated with hemolytic disease of the newborn (7).

Though anti-S usually occurs as a complete antibody it may also occur as the incomplete type acting at 37°C by indirect Coombs technique and being able to pass the placental barrier and cause hemolytic disease of the newborn (8). The antibody reacts with 56% of the white population.

In our patient the laboratory tests pointed towards the presence of incomplete (immune) anti-S in the mother's serum. The mother being S negative and the baby S positive. The cause of the severe hemolytic disease observed is believed to be due to isoimmunization of the mother to the factors S.

Summary

A severe case of erythroblastosis foetalis in the sixth child of an Rho (D) positive mother is described. The hemolytic disease was due to iso-immunization of the mother to factor S present in the baby's blood.

Resumen

Se informa sobre el caso de un recien nacido sufriendo de eritroblastosis severa. La madre y el infante eran Rho (D) positivos. La prueba de Coombs fue positiva. Estudio del suero de la madre reveló la prescencia de anti-S siendo ella S negativa y el bebé S positivo.

El recien nacido desarrolló bilirubinas muy altas en el suero: la máxima indirecta de 21.5mg%, la directa llegó a un valor de 18mg%. El paciente fue dado de alta en buenas condiciones después de recibir cuatro exanguino-transfusiones y una transfusión pequeña.

TABLE I: BLOOD TYPES

Type	Mother	Baby
D	+	+
C	+	+
E	−	+
c	+	+
e	+	+

TABLE III: BILIRUBIN AND HEMOGLOBIN DETERMINATIONS

		Bilirubin mg%			Hemoglobin (9/100ml)
		Direct	Indirect	Total	
6/7	8 AM	6.8	23.2	30.0	5.0
	4 PM	7.3	21.5	28.8	
		Exchange Transfusion			
Post exchange		2.7	7.5	10.2	
6/8	8 AM	3.6	10.8	14.4	
	10:30 AM	8.2	12.2	20.4	10.5
		Exchange Transfusion			
Post exchange		2.8	4.4	7.2	
6/9	2 PM	3.9	5.1	9.0	9.6
6/10	8 AM	12.0	9.6	21.6	
	4:30 PM	17.4	9.0	26.4	9.2
		18.0	13.0	31.0	
		Exchange Transfusion			
Post Exchange		4.9	2.9	7.8	
6/11	4 PM	9.0	6.6	15.6	8.0
		Exchange Transfusion			
6/12	7 AM	6.0	3.0	9.6	
6/13		6.8	3.2	10.0	7.5
		Transfusion 60cc			
6/15		3.4	2.0	5.4	11.3

TABLE II: IDENTIFICATION OF ATYPICAL ANTIBODY CELL NUMBER

	1	2	3	4	5	6	7	8	Auto
D	+	+	+	0	0	0	0	0	
C	+	+	0	+	0	0	0	0	
E	0	0	+	0	+	0	0	0	
c	0	0	+	+	+	+	+	+	
e	+	+	0	+	+	+	+	+	
f	0	0	0	+	+	+	+	+	
Cw	+	0	0	0	0	0	0	0	
V	0	0	0	0	0	0	0	+	
K	0	0	+	+	0	0	+	0	
k	+	+	+	+	+	+	+	+	
Fya	+	+	0	0	+	+	+	0	
Fyb	0	0	+	+	+	+	+	0	
Jka	+	+	+	0	0	+	0	+	
Jkb	0	0	0	+	+	+	+	+	
M	+	+	0	+	0	+	+	+	
N	+	+	+	0	+	+	+	+	
S	+	0	+	+	+	+	0	0	
s	+	+	+	+	+	0	+	+	
Lea	0	+	0	0	0	+	+	0	
Leb	+	0	+	+	0	0	0	+	
P1	+	+	+	+	+	+	0	+	
Lua	0	+	0	0	0	0	0	0	
Lub	+	+	+	+	+	+	+	+	
Xga	+	0	0	+	+	0	0	+	
Albumin	+	–	+w	+w	+w	+w	–	–	–
Ind. Coombs	+	–	+	+	+	+	–	–	–

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EDITORIAL

ALGUNOS APUNTES SOBRE LA OBESIDAD

La obesidad hace su aparición en la vida del Homo sapiens durante los días de la prehistoria cuando el cavícola aprendió a engullirse hasta la saciedad al no tener seguridad alguna sobre si podría hacerlo en los días por venir. El hombre cazador y su familia aprendieron a disfrutar del momento puesto que carecían de facilidades para la preservación de la carne y no habían desarrollado aún la técnica del cultivo de la tierra. Al correr de los siglos el hombre utilizó a plenitud los recursos que le ofrecía el reino vegetal y el reino animal, pero aún así, el espectro del hambre y la necesidad se yergue sobre muchos de nuestros coterráneos. Debido a esto, tanto en las culturas más primitivas como en los pueblos más adelantados, el comer asume una importancia desmedida como símbolo de status, una importancia que no se justifica desde el punto de vista de nuestra economía calórica. En nuestro mundo de Occidente este énfasis tan exagerado hace que la obesidad hoy día asuma proporciones alarmantes de problema de salud pública.

Hasta hace poco tiempo existían dos conceptos muy diferentes para explicar el desarrollo de esta enfermedad, a saber, la teoría de la obesidad de tipo exógeno y la teoría de la obesidad de tipo endógeno o metabólico. Los defensores de la teoría de la obesidad exógena mantenían que ésta era exclusivamente un problema de ingestión excesiva de alimento. Los propulsores del otro concepto mantenían que el paciente obeso sufría de un trastorno metabólico que le impedía utilizar o "quemar" adecuadamente el alimento ingerido. Las investigaciones básicas en el animal experimental y las pruebas de laboratorio más refinadas realizadas en el humano obeso, todo ésto producto de la última década, han podido reconciliar estos dos enfoques diametralmente opuestos y nos han permitido abordar el problema clínico de una manera más inteligente.

Los siguientes hallazgos básicos han surgido de los laboratorios y las clínicas que han dedicado sus esfuerzos a la solución de esta incógnita, a saber: 1) *Ratoncillos con lesiones farmacológicas y mecánicas del diencéfalo desarrollan una hiperfagia incontrolable la cual resulta eventualmente en un aumento exagerado de peso. Sinembargo, si el consumo de alimentos por el animal es restringido a cierto nivel calórico, los ratones recobran su peso normal. El Dr. Mayer, en cuyo laboratorio se llevaron a cabo estos experimentos, concluyó que este tipo de obesidad experimental correspondía al síndrome de la obesidad exógena en el hombre.* 2) *El examen patológico de estos ratones obesos demuestra la presencia de una hipertrofia con posible hiperfunción de la corteza de la grándula adrenal y una hiperplasia muy marcada de los islotes de Langerhans en el pancreas.* 3) *Mayer ha desarrollado en su laboratorio una cepa de ratones con hiperglicemia y obesidad congénitos. Estas dos condiciones están asociados en el mismo gene y parece que el síndrome es fácilmente transmitido de generación en generación. Este síndrome de obesidad e hiperglicemia probablemente corresponde a la obesidad humana debido a factores congénitos, concepto etiológico que al presente requiere mucho estudio y clarificación.* 4) *Estudios de la actividad insulínica en el suero de algunos pacientes obesos han demostrado la presencia en ayunas de altos niveles de esta hormona, además de una respuesta exagerada a la administración de glucosa por boca o por vena. Es muy fácil concluir que en estos sujetos la obesidad sea secundaria al efecto lipogenético de la insulina pero debo aclarar que no sabemos si este hallazgo es cause o resultado de la obesidad.* 5) *Debo recalcar que en la inmensa mayoría de los pacientes con obesidad ha sido imposible diagnosticar la presencia de una deficiencia endocrina, ya sea de origen tiroideo, pituitárico o gonádico. Es posible que en algunos pacientes el estado de obesidad crónico pueda dar lugar a cambios en la función de algunas de estas glándulas que a su vez contribuya a agravar la condición, pero hasta el presente existe muy poca evidencia al efecto.* 6) *El factor de actividad es de importancia extrema en la persona de edad mediana que reduce su ejercicio físico sin reducir su ingestión calórica. Este factor asume una importancia extrema en nuestra era de locomoción automovilística. Por lo general, esta combinación de factores resulta ser perjudicial al individuo pues la persona afectada pierde una gran cantidad de su tejido magro muscular el cual es sustituído por tejido grasoso.*

Para concluir, la obesidad es una enfermedad causada en la mayoría de los casos por factores familiares, ambientales o emocionales, o por una combinación de estos factores. Todos estos factores tienen como su denominador común un disturbio profundo en el balance de energía del cuerpo que resulta de una ingestión excesiva de calorías en conjunción con una disminución en el consumo de los mismas, lo cual da lugar a la acumulación y deposición excesiva de grasa en el cuerpo. El apetito está controlado por centros hipotalámicos los cuales están posiblemente bajo la influencia del nivel de glucosa en la sangre. Desórdenes del sistema nervioso central, del sistema endocrino y del metabolismo son causas muy raras de la obesidad. Sinembargo, cuando estos sistemas están comprometidos, la obesidad se encuentra acompañada de otras manifestaciones clínicas que hacen muy fácil la identificación de la enfermedad. Parece ser obvio, por lo tanto, que el tratamiento hormonal en la obesidad debe ser restringido exclusivamente para la corrección de los disturbios endocrinos o metabólicos y no como un medio para estimular la pérdida de peso en el paciente con obesidad simple. Por todas estas razones expuestas es imperativo que nosotros como médicos evaluemos los pacientes con obesidad de una manera organizada y detallada y que no tratemos de resolver el problema con un puñado de píldoras.

Agustín M. de Andino, M. D.

RESUMENES

UN CUENTO REPETIDO TRES VECES: EL CUIDADO DEL PACIENTE (*Caring for the patient—A thrice told tale) Alex M. Burgess, M.D. and Alex M. Burgess, Jr., M.D. New Eng. J. Med.* 274:1241-1244, 1966

Es el plan de los autores, el traer a la luz algunos de los defectos en la medicina moderna que resultan en cuidado del paciente que no es óptimo aún cuando se tome en consideración los avances de la medicina hoy en día. Así como en otros tipos de progreso, en la medicina hay ciertos tipo de regresión simultánea que afortunadamente es de magnitud insignificante, pero aún así es de importancia real. Es decir, que al tomar dos o tres pasos hacia adelante siempre estamos dando algunos hacia atrás. El propósito de los autores es acrecentar y dar importancia a estos pasos que se dan en dirección contraria a la buena práctica de la medicina.

Se han señalado algunos de los riesgos de hospitalización que son usualmente menores comparados con las ventajas de estar en un hospital, pero aunque de menor importancia, deben ser considerados y corregidos. Se ha discutido el énfasis dado a las múltiples pruebas de laboratorio a las cuales, a veces, se les da tanto o más peso que un historial bien tomado y un exámen físico bien hecho. Se mencionan algunos de los ejemplos en los cuales un nuevo medicamento ha tenido éxito avanzado seguido por evidencia más tardía de daño corporal que ha modificado sus indicaciones de uso o ha sido abandonado. Finalmente, se hace hincapié en la aparente pérdida del arte de tomar un historial bueno y de hacer un examen físico aún superior y de la tendencia de olvidarse de que el paciente es un ser humano, no un caso—un ser humano cuya presonalidad debe ser estudiada, cuyos temores y preocupaciones sean comprendidas, y cuya moral frente a su enfermedad debe ser mantenida.

La pérdida de interés de parte del médico en su práctica privada es un problema muy grande y tiende a relegarlo a él a una posición técnica e impersonal. El paciente, con sus temores y ansiedades, es el perdedor. Como dijo una eminente persona, "Nosotros, los pacientes, queremos un poco de humilde atención a una negligencia aristocrática". Con el desarrollo de grandes números de pruebas de laboratorio y otras formas de tratamiento, el médico se encara con una tentación casi irresistible de practicar una medicina que tienda a opacar su simpatía humana por sobre sus habilidades técnicas.

Luis Meléndez Poventud, M.D.

BALANCE METABOLICO EN PACIENTES OBESOS SOMETIDOS A UN REGIMEN DE AYUNO TOTAL, (Metabolic Balance of Obese Subjects During Fasting) Robert E. Bolinger, M. D., Barbara P. Lukert, M.D., Robert W. Brown, M.D., Lilia Guevara, M.D. and Ruth Steinberg, M. S. Archives of Internal Medicine 118:3-8, 1966.

Una serie de pacientes se sometió a un régimen de ayuno con y sin suplementos de calcio, proteína, potasio y sodio. Encontraron los autores que todos ellos desarrollaron hambre durante las primeras 24 horas. Esta desapareció y la anorexia coincidió con la aparición de la cetosis y cetonuria que estuvo presente en todos los casos. Algunos casos desarrollaron nausea y vómitos. Tres fueron tratados debido a acidosis metabólica. Hubo letargo y debilidad en casi todos los casos. No se reportó hipoglicemia y todos desarrollaron hiperuricemia sin que hubiese un caso de gota.

La pérdida de peso fue rápida con el ayuno

sin suplementos, y se demostró que era mayormente debida de agua (45%); pérdida de proteínas (35%) y que sólo un 20% de la pérdida de peso se debió a pérdida de grasa. Hubo desbalance nitrogenado, de calcio, sodio y potasio que se corregían si se le añadían cantidades apropiadas de éstos al régimen. De este modo se pierde menos peso durante el ayuno, pero se gana menos durante la fase posterior al ayuno debido a que se pierde menos proteína, menos sodio y más grasa.

Jorge Oms Rivera, M.D.

IMPLICACIONES DIAGNOSTICAS Y FISIOLOGICAS DE LA PRUEBA DE INFUSION DE ANGIOTENSINA (Diagnostic and Physiologic Implications of the Angiotensin Infusion Test) James A. Nicotero, M.D., Spero E. Moutsos, M.D., Eliseo Pérez-Stable, M.D., Henri E. Turrian, M.D., and Alvin P. Shapiro, M.D. New Eng. J. Med. 274:1464-1468, 1966.

La prueba de infusión de Angiotensina fue evaluada en pacientes hipertensos con estenosis de la arteria renal, hipertensión esencial y en controles normales. Su habilidad, a niveles posológicos diferentes, de separar pacientes con hipertensión renovascular como un grupo de otros pacientes hipertensos, fue confirmada. Sin embargo, su efectividad entre pacientes individuales, tanto en tratamiento como en pronóstico quirúrgico, no fue superior a otros procedimientos.

Pacientes con hipertensión esencial demostraron una sensibilidad aumentada a la angiotensina comparado con pacientes normotensos. La respuesta disminuida en el grupo renovascular puede entonces ser interpretada como representando una pérdida a esta hiperreactividad. Esta también está presente en pacientes con hipertensión maligna con mayor frecuencia. La respuesta presora a un polipéptido no relacionado, al análogo de la vasopresina (Pitressin), vasopresina fenilisinna, estaba también deprimida en hipertensión maligna así como en renovascular. Estos hallazgos sugieren una falta de especificidad de la hiporeactividad a la angiotensina e implican que representa una pérdida del mecanismo de hiperreactividad determinado periferalmente del paciente hipertenso en vez que un indicador de la angiotensina endogena circulante.

Luis H. Meléndez Poventud, M.D.

MALABSORCION EN ESCLERODERMA INTESTINAL (Malabsorption in Intestinal Scleroderma, Correction by Antibiotics) Kahan, I.J., Jeffries, G. H., Sleisenger, M.H., New Eng. J. Med., 274:1339-1344, 1966.

Los autores discuten cuatro casos de scleroderma intestinal con malabsorción. Cada paciente tuvo evidencia de scleroderma diseminado por muchos años antes del inicio de los síntomas, y en cada uno de los casos tuvo síntomas de enfermedad del esófago que precedieron a los síntomas intestinales. La malabsorción fué probada solamente por el uso de pruebas de absorción muy sensitivas, tales como excreción de D-Xilosa y de medidas cuantitativas de la excreción de grasa fecal.

La proliferación de bacterias en la luz del intestino delgado en sus prociones superiores fue sugerida por un aumento en la excreción del metabolito de triptófano, indican, luego fue confirmada por cultivos de contenido duodenal aspirado.

Tres de los cuatro pacientes respondieron dramáticamente a los antibióticos de amplio espectro con remisión de los síntomas y con mejoría en la absorción. Dos de los tres pacientes se han mantenido en antibióticos por periodos prolongados de tiempo (nueve y dieciocho meses respectivamente), con sentido de bienestar y aumento de peso. El desarrollo de resistencia bacteriana ha necesitado cambios periódicos en los antibióticos.

Es sugerencia de los autores que terapia prolongada por antibióticos sea útil en el tratamiento de escleroderma intestinal con malabsorción.

Luis H. Meléndez Poventud, M.D.

PROGNOSTICO DE LA BRONQUITIS CRONICA (Prognosis of Chronic Bronchitis) Geoffrey & Brinkman, Duane L. Block JAMA 197:1-8, 1966.

Los autores estudiaron 1,317 hombres seleccionados a base de ser trabajadores regulares entre las edades de 40 a 65 años. Fueron divididos a base de ocupación en: 1) no expuestos —trabajadores de hospital y oficinistas mayormente; 2) expuestos, pero no a sílica; 3) expuestos a sílica por más de 20 años, pero con placas de pecho normales; y 4) expuestos a sílica por más de 20 años con evidencia de silicosis por placas. Además fueron separados a base de la presencia de bronquitis crónica definida, como tos productiva de una cucharadita de esputo diario, por un periodo de 6 meses o más.

Al comparar la salud general, la habilidad para trabajar y la función respiratoria entre el grupo con bronquitis y los que no la tenían, no encontraron una diferencia significativa. Esto es contrario a los resultados de estudios anteriores, donde se demostraba un efecto adverso; lo que atribuyen los autores a que los casos estudiados eran personas con bronquitis crónica y no seleccionadas entre la población en general.

Norberto J. Arbona, M.D.

CONVERSION DE LA TAQUICARDIA VENTRICULAR POR METODO ELECTRICO (Electrical Conversion of Ventricular Tachycardia) Román W. DeSanctis, M.D., Dept. of Medicine. Mass. General Hospital y Harvard Medical School. JAMA, Febrero 22, 1965, *Vol.* 191 *No.* 8.

La terminación de la taquicardia ventricular por medio de choque eléctrico externo en 21 episodios ocurridos en 12 pacientes fue hecho electivamente. Todos estos casos habían sido tratados previamente con drogas que deprimían al miocardio, con resultados negativos. La taquicardia convirtió en 20 de los 21 episodios. Se usó corriente alterna en seis casos, con éxito en cinco casos. En los 15 casos restantes se usó corriente directa. El único fracaso no respondió a ninguna de las dos modalidades. Hubo un caso de fibrilación ventricular en cada grupo de pacientes, el que fue reconvertido a taquicardia ventricular con la aplicación de una segunda carga). El uso de corriente eléctrica externa probó ser un método efectivo y seguro para el tratamiento de la taquicardia ventricular cuando el uso de drogas ha fracasado o se estime que su uso sea peligroso para el paciente. En la experiencia del autor, su tratamiento para la taquicardia ventricular es el siguiente: si el paciente esta tolerando la arritmia bien, i. e. que no este hipotenso o en fallo cardiaco, le administra Pronestyl en dosis total de 2.0 gm., a razón de 50 mgm. por minuto, o Xylocaina en dosis de 1 mgm por Kg. de peso intravenoso. Si el paciente mostrase toxicidad a estas drogas antes de recibir la dosis total o si éstas no fuesen efectivas, entonces se pasa a usar la corriente externa. Esta políza del autor no es rígida y cada caso se evalúa individualmente. Es su opinión que si un paciente se encuentra hipotenso en fallo congestivo marcado cuando se ve por primera vez, la corriente externa se debe usar como primer método de terapia, a pesar de administrarle Xylocaina en lo que se hacen las preparaciones para la cardioconversión. A pesar de que una descarga de corriente directa programada tiene sus ventajas teóricas sobre la corriente alterna y es a la vez el sistema preferido del autor, al presente, la corriente alterna se puede usar como un método seguro y efectivo.

J. Arnaldo Bello, M.D.

REDUCCION DE PESO—UN ENIGMA (Weight Reduction—An Enigma) Joseph A. Glennon, M.D., Madison, Wis.

El autor de este trabajo sometió una serie de 199 pacientes que por lo menos tenían un 50% de sobrepeso a una dieta hipocalórica y luego los siguió en la misma mientras estaban en sus casas. En este grupo de pacientes encontró él que todos redujeron de peso mientras estaban hospitalizados. Subsiguientemente sólo un 12% perdió y mantuvo una pérdida de 20 libras. Un 6% perdió y mantuvo una pérdida de 40 libras. No se encontró diferencia en cuanto a edad, status socioeconómico o nivel de educación. Sólo a una persona le fue posible acercarse al peso ideal.

Jorge Oms Rivera, M.D.

CARTA

MEDICO (Medical International Cooperation Organization) fue organizado por los doctores Thomas Dooley y Peter D. Comanduras en el 1958 para ayudar a millones de personas en todo el mundo que nunca han recibido servicios médicos.

Las actividades de "MEDICO" incluyen ayuda por medio de personal, medicinas, equipo y adiestramiento a todos los países del mundo. Voluntarios de todas las especialidades participan en estas actividades, ya sea dando conferencias o sirviendo en hospitales. El propósito principal de estos programas es adiestrar el personal local para que ellos sean capaces de continuar la labor permanentemente.

Durante el mes de junio de 1966, tuve la oportunidad de servir en Honduras, parte del tiempo en la Escuela de Medicina de Tegucigalpa y parte en un hospital del interior localizado en Santa Rosa de Copán. Encontré allí una gran necesidad de médicos en todas las especialidades, pero mucho más en pediatría y medicina interna. Otros compañeros norteamericanos están sirviendo allí con gran entusiasmo y generosidad, pero tanto ellos como yo personalmente opinamos que la mayor contribución la podemos hacer los que sabemos el idioma del pueblo. Por esta razón, y por el hecho de que Puerto Rico tiene la suerte de contar con médicos tan buenos como los mejores en todas las especialidades, exhorto a aquellos compañeros que deseen hacer una buena obra a que consideren ésta como una de gran mérito. La dirección del programa es como sigue: MEDICO, A Service of Care, 2007 Eye St., N.W., Washington 6, D. C.

José E. Sifontes, M.D.

NOTICIAS

Locales

La Asociación Médica de Puerto Rico está interesada en obtener copias de los siguientes números del Boletín:

Años	*Meses*	*Años*	*Meses*
1903	enero a diciembre	1921	enero a diciembre
1904	" " "	1922	" " "
1905	" " "	1923	" " "
1906	" " "	1924	" " "
1907	" " "	1925	" " "
1908	" " "	1926	" " "
1911	" " "	1927	" " "
1912	" " "	1928	" " "
1913	" " "	1942	" " "
1915	" " "	1943	" " "
1917	" " "	1944	" " "
1918	" " "	1953	abril, junio y agosto
1919	" " "	1956	enero a diciembre
1920	" " "	1957	agosto
		1962	julio

Aquellos miembros de nuestra matrícula que tengan estos volúmenes y deseen donárselos a la Asociación Médica, favor de comunicarse con el Sr. Eulogio Bermúdez Vélez, Secretario de Redacción.

ECFMG EXAMINATIONS FOR 1966

Completed application must be received by ECFMG not later than November 15, 1966 for the Candidate to be admitted to the Examination to be given on February 15, 1967 and not later than June 13, 1967 for the candidate to be admitted to the Examination to be GIVEN ON September 13, 1967.

Council's new address:

3930 Chestnut St. Philadelphia, Pa. 19104, U.S.A.

Telephone: Area Code 215: 386-1300

Cable: Edcouncil, Philadelphia, Pennsylvania, U.S.A.

REUNIONES

Oct. 31—*Nov.* 2—Curso sobre arritmias cardiacas, por el Dr. Henry Maviott.

Noviembre 15-19.—Asamblea Anual Asociación Médica de Puerto Rico, Hotel San Juan, San Juan, Puerto Rico.

Noviembre 21-25.—8:00 p.m.— Conferencia por el Dr. Albert Montgomery Kligman auspiciada por el "American Academy of General Practice" y la Sección de Medicina General de la AMPR, en los salones de la Asociación Médica de Puerto Rico.

October 28-29—The American College of Physicians, Puerto Rico Regional, University of Puerto Rico School of Medicine, San Juan, Puerto Rico. Information: José A. de Jesús, M.D., P. O. Box 10659, Caparra Heights, P. R.



Efectivo el 1 de enero de 1967 es mandatorio incluir el número de zona postal en todas las direcciones. Aquéllas que no lo tengan no recibirán el Boletín.

Agradeceremos, por lo tanto, a nuestros correspondientes de quienes no tenemos su número de

zona postal, nos lo suministren para completar sus direcciones, de manera que puedan seguir recibiendo el Boletín de enero próximo en adelante.

Nacionales

AMERICAN COLLEGE OF PHYSICIANS POST GRADUATE COURSES

Oct. 3-7 — The Care of the Critically ill Medical Patient, Syracuse, N. Y.

Nov. 7-11 — Endoctrine And Metabolic Disorders, Brooklyn, N.Y.

Nov. 14-18 — Newer Aspects of Experimental and Clinical Allergy, Boston, Mass.

Nov. 28-Dec. 2 — Progress in Gastroenterology-1966, Philadelphia, Pa.

Dec. 5-9 — What the Internist Should Know About Cancer, New York, N. Y.

Dec. 14-17 Infectious Diseases, Pittsburgs, Pa.

AMERICAN THORACIC SOCIETY

Invitation:

The Medical Sessions Committee Invites Submission of Papers on all Scientific Aspects of Tuberculosis and Nontuberculous Respiratory and Cardio-Pulmonary Diseases for presentation at the 1967 Annual Meeting in Pittsburgh, Pennsylvania, May 22-24. Membership in the Society is not a prerequisite to participation on the program.

Abstracts:

Abstracts of papers should be submitted before JANUARY 5, 1967, to the Chairman of the Medical Sessions Committee. Abstracts of papers from investigators outside the United States will be most welcome provided they are in English and are submitted with the understanding that all papers accepted must be presented in English at the Annual Meeting. All abstracts will be reviewed by the Medical Sessions Committee. Selection will be largely based on the areas of interest suggested by you and others receiving this invitation. Reports of interesting or unusual cases will be considered for inclusion in case conferences.

Authors will be notified by FEBRUARY 10, 1967, if their papers have been accepted for presentation.

Abstracts selected for presentation at the Annual Meeting will be published in *The American Review of Respiratory Diseases*. Medical papers presented at the meeting may be submitted to *The American Review of Respiratory Diseases* by the author if he so desires for publication after the Annual Meeting.

Papers presented at the Annual Meeting must be original contributions not previously presented or published.

ESSAY COMPETTION

A competition for a $250 award for the best manuscript submitted by a medical student, intern or resident on any subject pertinent to and concerning occupational health has been announced by the Central States Society of Industrial Medicine and Surgery. The contest closes at midnight on December 31, 1966.

A second competition, open only to residents in occupational medicine, is announced by the Industrial Medical Association. The award, consisting of an embossed scroll, will be presented at the Association's annual meeting to the author or authors of a paper published in the open literature on a subject germane to occupational medicine which is judged to be the most outstanding of those submitted. Reprints entered in the competition must be published during 1966 and submitted prior to January 15, 1967.

Both contests will be judged by members of the Committee on Merit in Authorship of the Industrial Medical Association. The criteria will be largely based on clarity, validity, objectivity, originality and style. Complete contest rules may be obtained from: Industrial Medical Association, 55 East Washington St., Chicago, Ill., 60602.

EPILEPSY

Medical progress and changes in attitudes and laws have made it possible for most epileptics to lead a normal life today. But others are still the victims of ignorance, fear, and superstition.

The facts about epilepsy, its treatment, and studies of the records of epileptics in such activities as working and driving, are summarized in a new Public Affairs Pamphlet entitled *Epilepsy — Today's Encouraging Outlook*. The authors, who worked with a special committee of Epilepsy Association of America in preparing the manuscript, are Harry Sands, Ph.D. and Jacqueline Seaver. The pamphlet is available for 25 cents from the Public Affairs Committee, 381 Park Avenue South, New York, N.Y. 10016.

DIETARY FATS

No radical changes in the American diet are warranted on the basis of present knowledge about the role of food fats in cardiovascular disease.

This conclusion was drawn in a recent report on "Dietary Fat and Human Health" issued by the Food and Nutrition Board of the National Academy of Sciences-National Research Council (NAS-NRC).

It is essentially one of the major conclusions reached by the Council on Foods and Nutriton of the American Medical Association in reports issued in 1962 and 1965. The NAS-NRC report is a revised and updated version of a document first published in 1958.

The 1965 report by the AMA Council reaffirmed its 1962 position that "there is not sufficient information available at the present time to warrant a change in the American diet aimed at preventing heart disease in the general population".

General agreement also is found in the NAS-NRC and AMA Council reports on criteria for limiting food fats in the diet.

The Council on Foods and Nutriton said in 1965:

"The Council notes that after puberty, American men, and to a lesser extent women, show a progressive rise in serum betalipoprotein content and the associated cholesterol, phospholipid, and triglycerides until age 60. Present knowledge suggests that this rise is associated with an increasing risk of coronary disease in men, whereas women are relatively protected until after menopause. The Council believes that the development of coronary disease in young American men may be attributed to a combination of unfavorable genetic and environmental factors. One environmental factor of importance to the genetically predisposed person may be the American diet."

The Council recommended that physicians advise persons with an abnormal excess of fatty materials in the blood to undertake diet therapy aimed at lowering the concentration.

"In addition", the Council said, "it recommends that physicians consider offering similar diet modifications to young men vulnerable to coronary disease in an attempt to prevent the rise of serum lipids which, in time, might put them into high-risk categories."

The Food and Nutrition Board of NAS-NRC points out in its report that: (1) fats play a vital role in nutrition, and any drastic reduction in fat consumption would alter body metabolism in unpredictable and possibly harmful ways; (2) no positive case has ever been made against dietary fats as a direct cause of cardiovascular disease; (3) nevertheless, the attractiveness and availability of rich or fatty foods place the American consumer in some danger of overnutrition and dietary imbalance.

Therefore, the Board says: "Until we learn more about which fats are desirable nutritionally, the Board recommends that the American consumer should partake of the foods that make up a varied, adequate, and not overly rich diet and maintain a normal body weight by judicious control of caloric intake and by daily exercise."

For many Americans, says the Board, a moderate reduction in total fat intake and some substitution of polyunsaturated for saturated fat may be indicated for purposes of dietary balance. "The degree to which this is done must be judged on an individual basis and, in adjustment of the diet, other changes of caloric and nutrient intake must be taken into consideration," according to the Board.

The AMA Council recommends that adjustment of dietary intake and the ratio of saturated to polyunsaturated fats be made under the supervision of a physician.

EXAMINING PALMS

Heart disease and other birth defects are among health problems now being studied by examining an infant's palm and foot prints. Two articles in the August 29 Journal of the American Medical Association describe progress in the comparatively new science of dermatoglyphics, the study of skin patterns.

These crease patterns form during the first three months of pregnancy, and remain unchanged throughout an infant's life. The palm prints of most normal, healthy babies are similar; variations from these normal patterns may give clues to disease and its cause.

There is good evidence that many rubella-damaged infants can be identified at birth by palm-print examination, say two University of Minnesota investigators in one J.A.M.A. report. They found

significant alterations in the palm prints of 28 rubella-damaged infants.

It may never be possible, however, to use dermatoglyphics to identify rubella-damaged infants before birth. Even normal palm and foot prints vary widely, the investigators point out, and examination of a fetus is difficult. Only when there are other symptoms of rubella damage can dermatoglyphics be used to reinforce a suspicion of rubella damage, they said.

In a second J.A.M.A. report, two Japanese physicians add further evidence that palm prints can be used to determine the general cause of heart disease.

Among Japanese patients with heart murmurs, the investigators found a significantly greater number of palm-print abnormalities among those with congenital heart disease than among persons who acquired heart disease after birth. These findings agree with results of earlier studies of Caucasian and Negro patients.

Thus, unusual palm prints may have a close relationship to genetic disease, the authors suggets. They said much more might be learned about congenital heart disease if a patient's family background were studied, using his relatives' palm prints as a guide.

The outhors, Tsunekazu Takashina, M.D., of Yodogawa Christian Hospital, Osaka, and Susumu Yorifuji, M.D., of Kobe University School of Medicine, Kobe, studied 1,312 pairs of palm prints of Japanese and Caucasians. Among 44 patients with congenital heart disease they found that 64 per cent had palm-print abnormalities, compared to only 17 per cent of 362 patients with acquired disease.

The medical knowledge to be gained by a careful study of skin patterns has no relation, however, to the "age-old seamy practice of palmistry," said a J.A.M.A. editorial.

Though not a product of false science, dermatoglyphics did not entirely escape pseudo-scientific influences. One that clung to it for some time is the concept of "mongolism."

First described 100 years ago, the syndrome of "mongolian idiocy" became associated with finger and palm analysis. Later, and elaborate theory was developed to "prove" that mongolian races had a simian palm crease, and thus were somehow inferior to Caucasians.

"Although this prevalence (of a simian hand crease) has since been refuted by several investigators, the concept of 'mongolism' persisted for a long time, to the detriment of medical dermatoglyphics," the editorial said.

A sidelight of the report by the two Japanese physicians is that it revealed "no significant difference in palm prints" between Caucasians and Japanese, the editorial said.

BIRTH-CONTROL INFORMATION FOR WELFARE PATIENTS

Many women who desperately want and need birth control information often cannot get it—simply because welfare agencies refuse to provide this service.

This indictment of "second-class medical care" for welfare patients is contained in a signed editorial in a recent issue of the Journal of the American Medical Association. The editorial was prepared and signed by John C. Ballin, Ph.D., secretary to the AMA Committee on Human Reproduction.

"Women able to afford a private physician can get adequate information and instruction on methods of fertility control as well as the actual contraceptive supplies. They assume the right to these services as part of first-rate medical care," Dr. Ballin writes.

"Yet, the indigent woman who must go to public health and welfare agencies is all too often discriminated against by being denied these services which she so desperately needs and wants. This is second-class medical care at best."

There are several reasons, says Dr. Ballin.

In some cases, birth control services are prohibited in tax-supported health facilities by statute, or are omitted from the programs.

In other cases, physicians and public health officials lack the courage to break on unwritten rule against mentioning birth control.

"Whatever the cause," writes Dr. Ballin, "the net result is that impoverished women continue to have babies that they do not want and cannot support, either psychologically or financially."

All over the world, individuals and groups have endorsed the principle of responsible parenthood,

Dr. Ballin points out. In 1964 the AMA House of Delegates stated that "An intelligent recognition of the problems that relate to human reproduction, including the need for population control, is more than a matter of responsible parenthood; it is a matter of responsible medical practice."

The AMA also has stated as a matter of official policy that "the prescription of child-spacing measures should be made available to all patients who require them, consistent with their creed and mores, whether they obtain their medical care through private physicians or tax- or community-supported health services."

Most major legal barriers to dissemination of birth-control information have now been removed in this country, Dr. Ballin notes. A 1965 decision of the U.S. Supreme Court declared unconstitutional a Connecticut ban on the use of contraceptives. In May of this year the Massachusetts legislature repealed a state law which prohibited the sale or dissemination of information on contraceptives.

In addition, the AMA House of Delegates has urged that appropriate legislation be enacted, wherever necessary, so that physicians can legally give contraceptive information to patients.

Thus, Dr. Ballin appeals to physicians, public health workers, and municipal authorities to "show greater courage in breaking down the barriers to provide birth control services in all public health and welfare programs and in municipal hospitals."

"This is not, or should not be, a religious issue." he says. "It is, instead, a matter of giving first-class medical service to all our citizens. Certainly in a country which prides it self on having the world's finest system of medical care, we can no longer afford to deny this integral part of comprehensive health care to the very segment of our population that needs it most."

VIRUS DISEASES EFFECTS ON PREGNANCY

The relationship of premature birth to a mother's virus diseases during pregnancy, such as mumps, chickenpox, hepatitis, measles, and German measles (rubella), are reported in the current (August 29) Journal of the American Medical Association.

The various diseases had somewhat different effects on unborn children, the large-scale survey shows. The study, done in New York City between 1957 and 1964, involved 1,652 mothers. Premature children of mothers infected with virus diseases were compared with the premature infants of mothers who did not have these diseases during pregnancy.

By far the most damaging virus disease is rubella, the study shows. It caused more premature births, more fetal deaths, and more birth defects than any of the other virus diseases.

Why the other diseases cause prematurity isn't entirely clear, the report said. Rubella is the only one known to infect the fetus itself. The damaging effects of mumps, hepatitis, measles, etc., may be due to the mother's high fever, metabolic changes, or toxic products produced during disease.

Increases in prematurity and infant deaths were limited to the early weeks of pregnancy in the case of rubella, and late in pregnancy for mothers who had hepatitis.

In measles cases, ill effects were limited to prematurely born infants; measles did not cause a significant increase in fetal deaths.

On the other hand, when mothers had mumps there was an increase in early-pregnancy fetal deaths, but few other complications. These early-pregnancy deaths may have been related to the effects the mumps virus has on the hormonal and placental changes that occur at this time, the authors said.

In chickenpox, there was no significant increase in early fetal deaths, stillbirths, or prematurity except in unusual cases.

Of mothers who had a virus disease in the first 12 weeks of pregnancy, 21.5 per cent gave birth to infants considered underweight. Only 4.4 per cent of those infected after the first 12 week of pregnancy had underweight babies.

Here are the survey's findings on each disease:

German measles (rubella)—Caused the greatest number of stillbirths, birth defects, premature births, and underweight births. Prematurity was limited to those mothers infected in the first 12 weeks of pregnancy.

Measles — A significant number of premature babies were delivered by mothers who had measles. The stage of pregnancy at which they contracted measles had little effect on prematurity.

Hepatitis — An increase in prematurity and infant mortality, but limited to mothers who had the disease late in pregnancy.

Chickenpox — Few complications, except in unusual cases.

Mumps — Increase in early-pregnancy fetal deaths; few other ill effects.

The study of the relationship of birth defects and virus infections is still incomplete, pending hearing and mental-development tests when the children reach age 5. Preliminary findings, however, indicate that only rubella causes a significant number of birth defects, and these are caused only if the mother is infected during the first 12 weeks of pregnancy.

Authors of the report are Morris Siegel, M.D., and Harold F. Fuerst, M.D., of the Department of Environmental Health Medicine and Community Health, State University of New York College of Medicine, and the Bureau of Preventable Disease, Department of Health, New York City.

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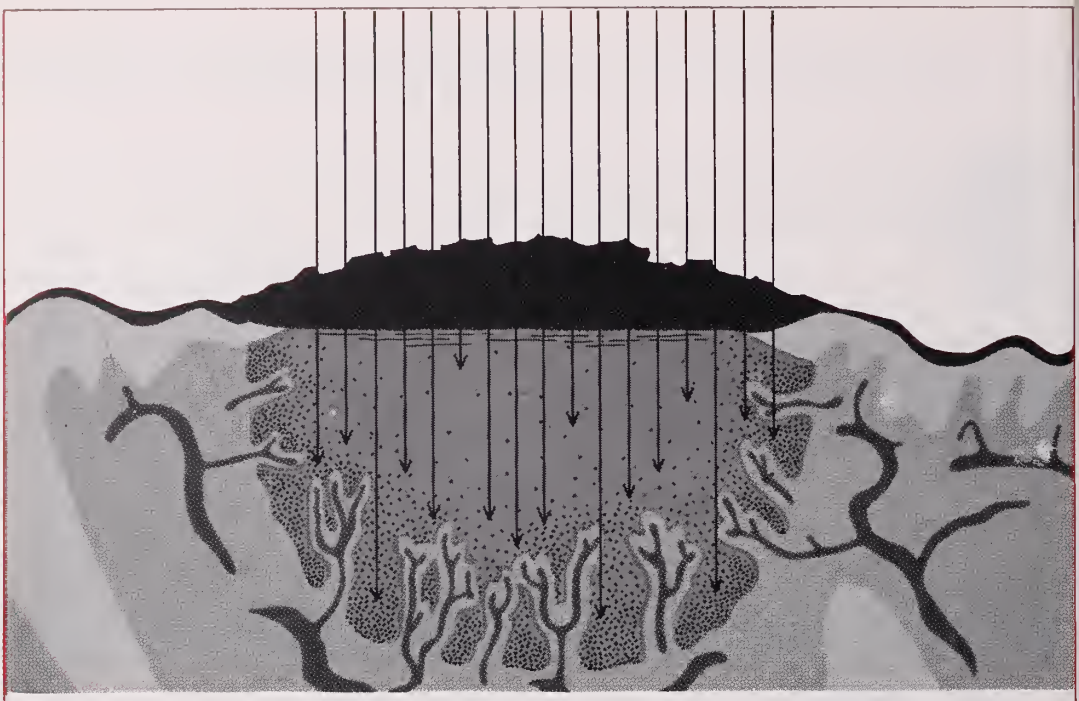
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1. Frohman, I. P., A New Antitussive Agent, M. Times, 88:924 August, 1960.

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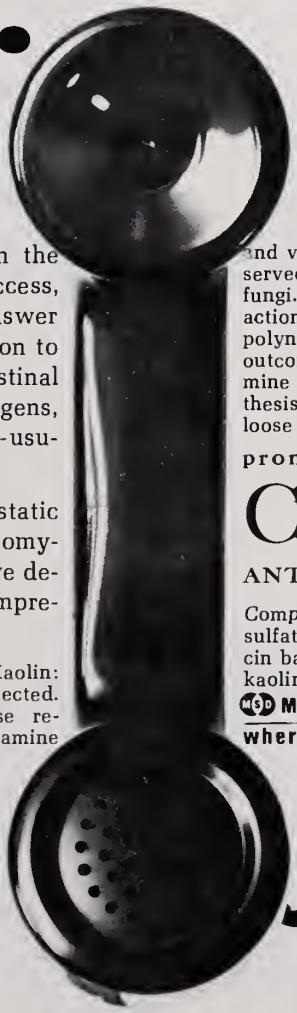


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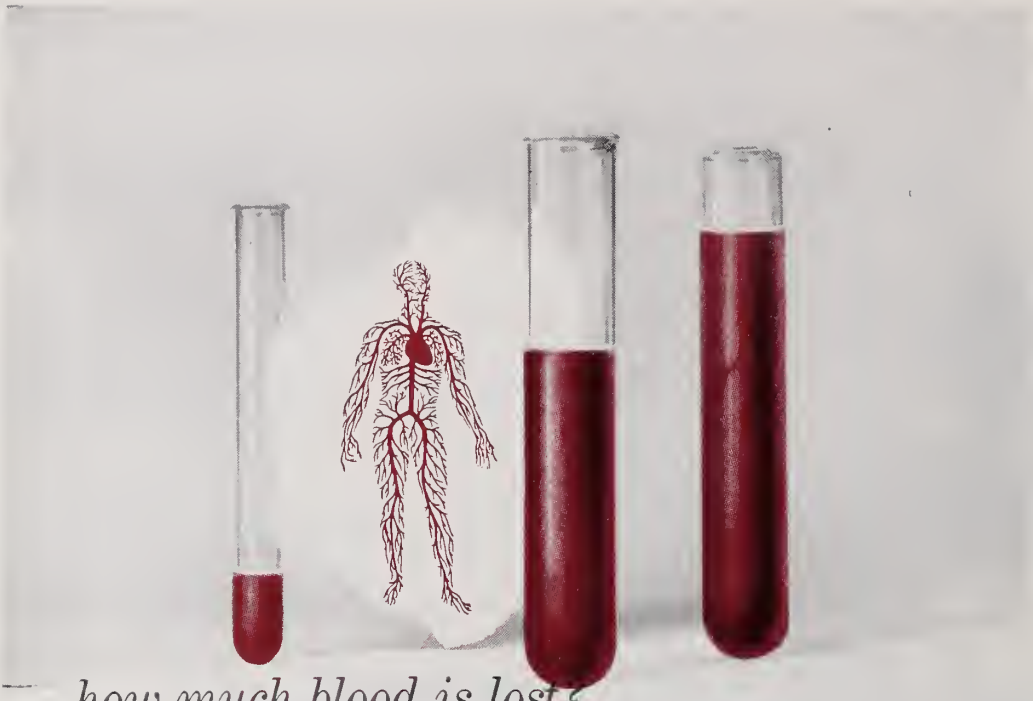
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References: 1. Persun, L.: Laryngoscope *74*: 260-266 (Feb.) 1964. 2. Fulton, G.P., *et al.:* Venoms: Am. Assn. Advancement of Science, 1954.

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References: (1) Clarkson, I. S., and Le Pere, D. M.: Angiology *11*:190-192 (June) 1960. (2) Kaindl, F.; Samuels, S. S.; Selman, D., and Shaftel, H.: Angiology *10*:185-192 (Aug.) 1959. (3) Kaindl, F.; Partan, J., and Polsterer, P.: Wien. klin. Wchnschr. *69*:186-191 (March 16) 1956. (4) Billiottet, J., and Ferrand, J.: Semaine méd. *78*:635-637 (May 20) 1958.

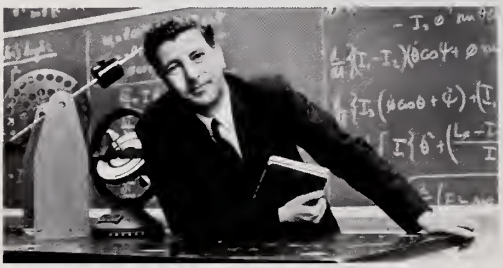
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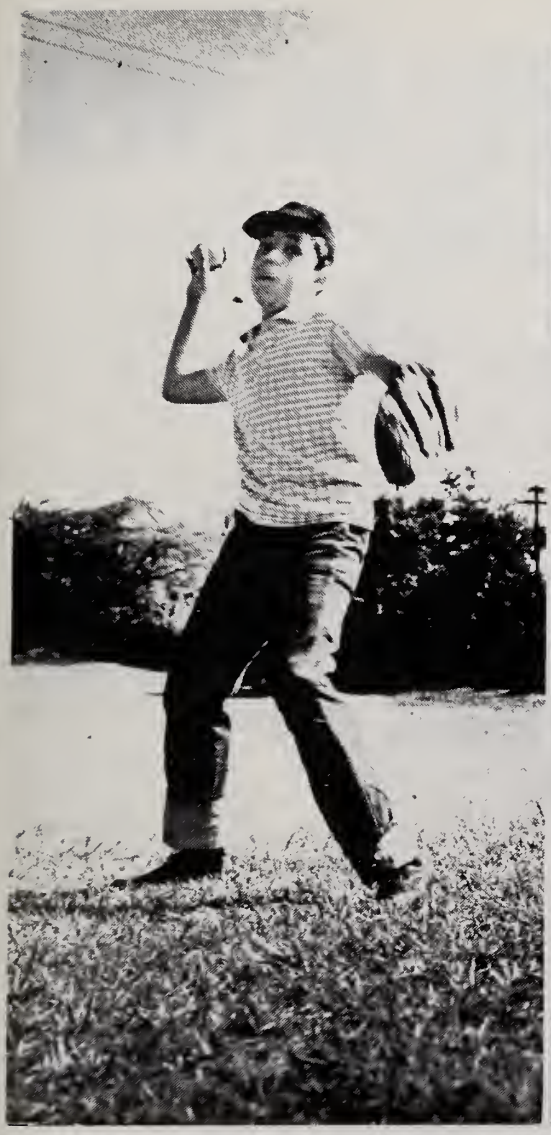
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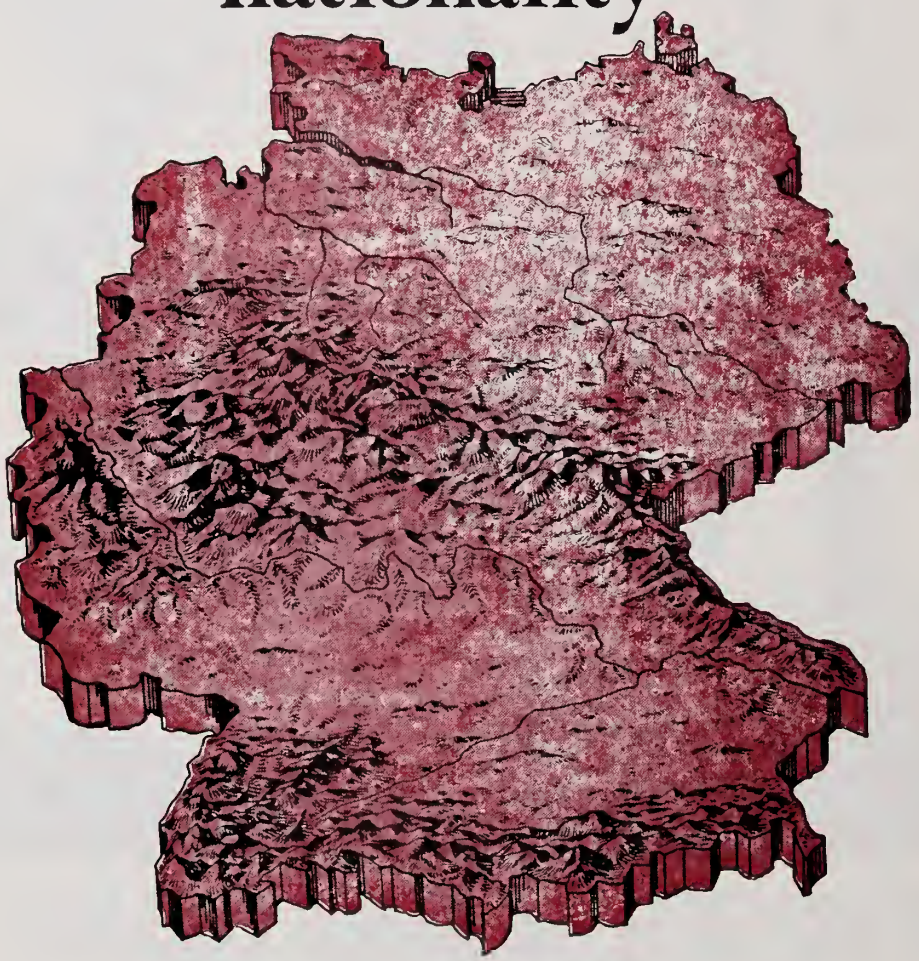
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PAROXYSMAL NOCTURNAL HEMOGLOBINURIA

STUDY OF FIVE CASES

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Paroxysmal nocturnal hemoglobinuria (PNH) is a rare acquired chronic hemolytic anemia of unknown etiology. The disease is characterized by remissions and exacerbations. It has been described in all racial groups and in all age groups including childhood but it is more frequent in the third and fourth decades (1).

The symptoms in PNH are variable. Although hemoglobinuria is a classical finding some patients do not complain of this initially and in others it occurs rarely. Symptoms due to anemia are also a frequent presenting complaints but some patients do not present with anemia. Nausea, vomiting and abdominal pain may be the presenting symptoms in other patients (2). The physical findings are frequently those of anemia. Jaundice may be present during hemolytic crisis and the spleen is palpable in some patients.

In 1953 Crosby suggested that PNH had an incidence of 1 in 500,000 of the population (1). We have seen 5 patients at the University Hospital during the last 6 years, which is what is expected for our population, but we have knowledge of 5 additional cases in Puerto Rico. Since our populations is 2.5 million it seems that our incidence is twice the expected. We will present the clinical histories and laboratory studies done on our patients. A discussion of the pathogenesis of the hemolytic process and its management will follow.

From the Department of Medicine of the University Hospital, University of Puerto Rico School of Medicine, San Juan, P.R.

This study was supported in party by the NIH grants No. 5 TOI AM05302-05 (Hematology Training Grant) and No. 5 ROI AMO2776 (Study of Vitamin B-12 Metabolism in Tropical Sprue).

Material and Methods

Five patients in whom the diagnosis of paroxysmal nocturnal hemoglobinuria was made between January 1960 until the present time were studied. Four of these patients were referred to us for evaluation of refractory anemia. Only one patient was originally seen in our emergency room.

During the initial evaluation a complete blood count including a peripheral blood smear and a reticulocyte count were done. Bone marrow aspiration, a Coomb's test, sickle cell preparation and presumptive test for osmotic fragility were done routinely. The neutrophil alkaline phosphatase was measured by a modification of Gomori's original method (3) and the Ham test was done as originally described by Ham (4). The thrombin test was done as described by Crosby (5). The serum Vitamin B_{12} levels were measured by the *Euglena gracitis* method and the serum iron was done by a colorimetric

method*. The glucose -6-phosphate dehydrogenase determination was done with the commercial kit of Sigma (6). Iron stain of the bone marrow and the urinary sediment was also done in all patients.

The red blood cell survival was determined in 3 patients using radioactive Cr^{51}. The erythrocyte acetylcholinesterase was determined by a colorimetric method (7). The sugar water test was performed according to a recently described method (8). The autohemolysis test with and without glucose incubation was done in 4 patients (9). The hemoglobin electrophoresis was done by the conventional paper method.

The outstanding clinical aspects, routine laboratory tests and special studies are summarized in tables I, II, III and IV.

Case Reports

Case 1: This 44 year old mulatto man from Yabucoa, was admitted to the University Hospital on September 13, 1960 complaining of red urine since January, 1959. The onset of the illness was characterized by the passage of red urine in the first morning specimen, the color of the urine clearing during the rest of the day. In May of 1959 he developed marked weakness and giddiness. He was hospitalized at the Yabucoa Hospital where he was found to be extremely anemic and was given three blood transfusions. Following discharge from the hospital he continued passing red urine three to four times a week. In February 1960 and again in August 1960 he was hospitalized at the Fajardo District Hospital. Complete urologic evaluation, which included an I.V.P. and a cystoscopic examination, was negative. He was given several transfusions and then transferred to the University Hospital for further study. The family history was revealing in that his father died of pulmonary tuberculosis at age 60. The past history was non contributory, The systemic review revealed occasional frontal headaches, blurred vision for the last year, nocturia and diurnal frequency.

Physical examination revealed a well developed, undernourished, chronically ill looking, middle aged man. The only positive physical findings were hyperthropic cryptic tonsils, a grade I aortic systolic murmur and a barely palpable splenic tip.

The laboratory data revealed the following: The urine was red colored and contained faint traces of albumin. The BUN was 13.2 mg.%; glucose, 101 mg.%. The prothrombin time was 16.5 seconds with a control of 14.5 seconds. The VDRL was negative. The total serum bilirrubin was 0.4 mg.% with a direct fraction of 0.2 mg.%. The red cell count was 1.31 millions, hemoglobin 4.6 Gms., reticulocyte count 46.2%. The white cell count was 1,450, the differential count showed 1 metamyelocyte, 6 bands, 40 segmented, 41 lymphocytes, 11 monocytes, 1 eosinophile and 2 nucleated red cells per 100 white cells counted. The platelet count was 60,000. The red cell morphology showed marked macrocytosis and polychromatophilia and many stippled cells. The bone marrow showed a very striking normoblastic erythrocytic hyperplasia. Iron stain of the bone marrow showed marked increase in stainable iron. Iron stain of the urinary sediment showed marked hemosiderinuria. The plasma hemoglobin was 94 mg. % (Normal up to 5 mg. %). The Ham test (acid hemolysis) was strongly positive. The thrombin test (Crosby test) was positive. Progressive hemolysis was observed on coagulated blood left standing at room temperature. The blood plasma and the urinary sediment were of brownish "tobacco" color. The sickle cell preparation, the presumptive test for increased osmotic fragility and the Coomb's test were all negative. The alkaline phosphatase score of the mature granulocytes was zero. The red blood cell survival with Cr^{51} was 7 days (normal 28 days). The urinary excretion of the radioactive material in 72 hours was 19.3% (normal 1%). The blood loss in the urine during a 6 day period was 210 cc. The average excretion of hemoglobin in the urine during a 4 day study period was from 6:30 A.M. to 6:30 P.M., 388 mg. and from 6:30 P.M. to 6:30 A.M., 823 mg.

The patient was given 2 transfusions of packed cells and was discharged. He was followed in the OPD clinic for 6 months and then failed to return.

He was recently called back and returned 5 years after the last clinic visit. He was being fol-

* *Diagnostic Reagents, Columbus, Ohio.*

lowed at Fajardo District Hospital receiving two transfusions per year. He was very pale but had no complains. The spleen was not palpable. The hemoglobin was 6 gms.; WBC 3,450, platelets 183,000 and reticulocytes 46%. The Ham test and sugar water tests showed striking hemolysis. The RBC glucose-6-phosphate dehydrogenase was normal. The erythrocytic cholinesterase activity showed moderate inhibition. The autohemolysis test was positive with and without glucose incubation. He had normal adult hemoglobin. The serum vitamin B_{12} was 160 uugms/ml. The serum iron was 15 mcgms/100 ml. and the urine hemosiderin was strikingly positive. A bone marrow aspiration showed normoblastic erythrocytic hyperplasia, eosinophilia and increase in mast cells. The iron stain revealed no stainable iron. Because of the iron deficiency he was placed on oral ferrous sulfate therapy.

Case 2: This 62 year old colored male was first seen on October 19, 1955 complaining of anemia. In 1947 he had a sudden paralysis of the lower legs which subsided rapidly. A similar episode occurred in 1951 and 5 months later he noted weakness and increasing pallor. He was studied by a local physician who diagnosed aplastic anemia because of the finding of pancytopenia. He was later referred and re-studied by two other physicians who confirmed the diagnosis but one of these observers noted the presence of splenomegaly. The patient was given blood transfusions and his blood requirements were approximately one pint of blood every two or three months. However, in 1955 he noted more active blood requirements and required approximately 1 pint every 1-½ months. He had a total of 45 blood transfusions up to 1955. Blood studies in 1955 showed a red cell count of 1.39 million; hemoglobin, 5.4 grams; WBC 2,150; platelets 30,000; reticulocyte count 4%. Peripheral blood showed polychromatophilic macrocytes and 2 normoblasts/100 WBC. Hypotonic fragility, urine sediment for hemosiderin and sickle cell preparation were reported negative. The patient refused a bone marrow aspiration. From 1955 until July 1960 the patient was seen infrequently and during the course of this time he had numerous transfusions and for short intervals received treatment with small doses of prednisone (5 ms. t.i.d.).

When seen in July 1960 the patient stated that his blood requirements were 1 pint per month and that following his last blood transfusion he had passed dark urine. He had noted no bleeding manifestations, except for occasional bright red blood in the stools. Systemic review was essentially negative. Family history was negative. In the past medical history the patient claimed that he had kidney disease in the past, but he had gotten well. No history of exposure to chemicals could be obtained.

On physical examination he was a well nourished, well developed, colored male who appeared very pale. There was a questionable icteric tinge to the sclerae. The rest of the examination was negative except for the presence of a palpable spleen.

The original hematological evaluation revealed a hemoglobin of 6.8 g., RBC count 1.83 million/mm³, reticulocyte of 15%, platelet count of 38,000/mm³. The WBC was 4,200 with a differential count of 50% segmented, 3% stabs., 39% lymphocytes and 8% monocytes. The sickle cell preparation and the presumptive osmotic fragility were negative. The urinary sediment was brownish and there was a striking amount of stainable iron. The bone marrow showed erythrocytic hyperplasia (Fig. 1). The iron stain of the bone marrow showed increased amounts of stainable iron. The Ham test and the thrombin test were positive. Hemoglobin electrophoresis showed normal adult hemoglobin.

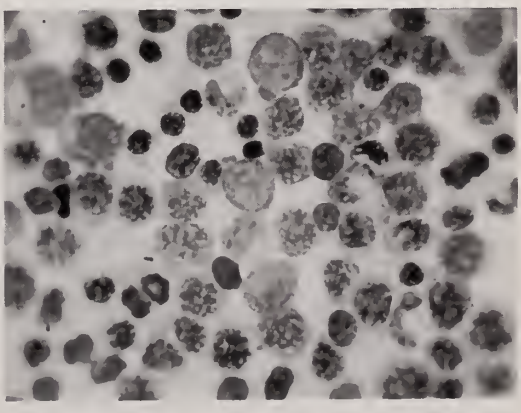


Fig. 1: Photomicrograph of the bone marrow showing erythrocytic hyperplasia. (X 500).

In 1961 he was admitted to the University Hospital with an acute viral illness. He was suspected of having a hypoplastic crisis which was confirmed by the bone marrow aspiration (Figure 2). He received wide spectrum antibiotics and recovered. The bone marrow was hyperplastic at the time of discharge.

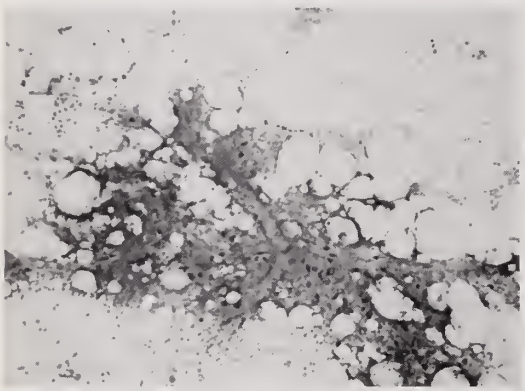


Fig. 2: Low power photomicrograph of the bone marrow during the aplastic crisis. Notice the hypocellularity of the preparation. The dark dots are the increased mast cells (50).

Subsequently the patient was admitted to the Rodríguez U.S. Army Hospital where a complete metabolic study was done. The hematologic studies were unchanged. The urinalysis revealed 2+ proteinuria and 5–7 RBC/h.p.f. The total bilirubin was 1.3 mg. with 1.4 mg. indirect. The SGOT was 152 and the SGPT 42. The total protein was 8.37 g. % with 5.07 g. of albumin. The serum iron was 362 mg. %. The BUN was 15 mg. % and the electrolytes were normal. The plasma Hgb. was 70 mg. %. RBC survival and iron turnover studies were done, but the results are not available.

Recently we found a positive sugar water test and a marked inhibition of the erythrocyte acetylcholinesterase activity. The G-6-PD test was normal. The bone marrow showed erythrocytic hyperplasia with increase iron stores. The urinary hemosiderin was increased. The serum iron was 120 micrograms/100 ml and the serum vitamin B_{12} was 220 uugms/ml. He is receiving one blood transfusion every 2 to 3 months.

Case 3: This 46 year old white woman was seen in the emergency room of the University Hospital in March 1963 with a history of progressive weakness for seven months. She developed diarrhea one week prior to her visit and her weakness worsened. She complained of easy bleeding from her gums but denied hematemesis, hematuria or rectal bleeding. She had loss of hearing for about 3 months. Her family history and past history were non contributory. On physical examination the BP was 164/96 and the pulse 120/min. She was obese but looked chronically ill. The spleen was palpable. She refused admission to the hospital.

Three months later she was seen again and had a complete hematologic evaluation. The hemoglobin was 2.0 g.; RBC count, 770,000/mm^3; WBC, 2,650 with 52 polymorphonuclears, 41 lymphocytes, 6 monocytes and 1 eosinophil. The peripheral blood showed 1 nucleated red blood cell/100 WBC and low platelets. The platelet count was 10,000/mm^3 and the reticulocytes 14%. The bone marrow showed erythrocytic hyperplasia with normoblastic development. Toxic granulation of the granulocytic precursors was noticed. The iron stain showed increased storage iron. The Coomb's test, the presumptive osmotic fragility and the sickle cell preparation were negative. The urine of a brownish "tobacco" color and urinary hemosiderin was increased. The Ham test and the thrombin test were positive. The vitamin B_{12} level was over 6,000 uug/ml. The BUN was 7.75 mg.%. The alkaline phosphatase stain of the granulocytes was 366 (normal 20-60). The patient was lost to follow up and is presumed dead.

Case 4: This 33 years old mulatto man was in good health until 1960 when he became weak, tired and icteric. He was hospitalized in Arecibo District Hospital and had several studies performed, but a final diagnosis was not established. He was told to have a low hemoglobin and was given 4 blood transfusions. He did well for 1 year when the same symptoms recurred and he was again hospitalized at Arecibo District Hospital and 2 blood transfusions were given. He improved for about one year and again the symptoms recurred for which reason he was referred here in November 1963.

His past history and family history were not revealing. On physical examination he was pale

and had a grade II apical systolic murmur. The spleen was not palpable.

The hemoglobin was 6.0 g; the WBC was 3,250 with 48% polymorphonuclears and 52% lymphocytes. The reticulocytic count was 15.8%. The peripheral blood showed macrocytosis, polychromatohilia and anisocytosis. The urinalysis was normal. The FBS was 87.5 mg.%, the BUN 12 mg.% and the total bilirubin 0.3 mg.%. The stools were negative for occult blood, ova and parasites. The total protein was 7.25g with 4.9g. of albumin and the alkaline phosphatase was 7.0 King-Armstrong units. The sickle cell preparation and the Coomb's test were negative. The urine sediment was of a brownish "tobacco" color and the hemosiderin was strongly positive. The Ham test and the thrombin test were also strongly positive. The bone marrow showed erythrocytic hyperplasia and marked diminution in storage iron which was suggestive of blood loss. The patient was given one unit of packed cells and referred to his private physician for follow up. He was again hospitalized in the Arecibo District Hospital in May 1964.

When seen in August 1966 he was asymptomatic with hemoglobin of 13 g. The Ham test was slightly positive and so was the sugar water test. The cholinesterase activity of the red cells was normal, but the alkaline phosphatase stain of the granulocytes was zero. The urine hemosiderin was positive. The serum vitamin B_{12} was 464 uug/100 ml. A red blood cell survival showed a half-life of 26 days. The autohemolysis test was positive with and without glucose incubation. His hemoglobin was normal AA. The bone marrow was compatible with mild hemolysis, but there was no stainable iron in the bone marrow. The serum iron was 80 mcgms/100 ml. He was considered to have a partial iron depletion and was given oral ferrous sulfate.

Case 5: This 46 years old white man was in good health, while living and working in New York City, until May 28, 1964. He developed a dizzy spell and blurred vision suddenly, for which reason he was taken to a hospital and was hospitalized for 3 weeks. He was told that his hemoglobin was low and all other studies including stomach and chest X-rays were normal. He returned to Puerto Rico and was treated by a private physician with vitamin B_{12} parenterally. Except for dizziness he denied any other symptomatology. He was referred to Arecibo District Hospital in October 1964 where he was described as obese and pale, but had no other physical abnormalities. His hemoglobin was 6.7 g.; WBC, 5,900 with 49% polymorphonuclears and 48% lymphocytes. The RBC count was 2,300,000; platelets, 156,400 and reticulocytes 9.4%. The urinalysis showed 2+ and 18 to 25 RBCI h.p.f. The stools were negative for occult blood, ova and parasites. The serum bilirubin was 0.7 mg % with 0.40 mg. indirect. The total protein was 6.9 gms/100 ml with 4.8 gms. of albumin.

In December 1964 he was referred to the University Hospital where a history of dark urine in the morning was elicited. He had no adenopathy or hepatosplenomegaly. The hemoglobin was 8.5 g.; WBC. 5,650 with 48% polymorphonuclear, 38% lymphocytes, 7% monocytes, 5% eosinophils and 1% basophils. The peripheral smear showed 3 nucleated red blood cells per 100 white blood cells, polychromatophilia and some basophilic stippling. The reticulocyte count was 45% and the platelet count 208,000. The bone marrow showed erythrocytic hyperplasia and increased stainable iron. The sickle cell preparation was negative and the hemoglobin electrophoresis showed normal adult AA hemoglobin. The presumptive osmotic fragility was negative. The glucose 6-phosphate dehydrogenase concentration of the red blood cells was normal. The Coomb's test was negative. The urinary sediment was of the brownish "tobacco" color and the hemosiderin stain was strongly positive. The Ham test and the thrombin test were positive. The urinalysis revealed 2+ proteinuria and a BUN was 14.5 mg.%. The patient has been fairly asymptomatic except for anemia requiring transfusion every 3 or 4 months.

In August 1966 his hemoglobin was 7.5 g. and he was asymptomatic. An alkaline phosphatase stain of the granulocytes was zero. The sugar water test was positive and the autohemolysis test was also positive. The red cell cholinesterase showed moderate inhibition. The serum iron was 30 mcgm/100 ml. and the vitamin B_{12} was 381 uug/ml. The bone marrow showed erythrocytic hyperplasia as seen in hemolysis and also evidence of iron deficiency. There was no stainable iron in the bone marrow and the urine hemosiderin was positive. The red blood cell survival gave a T1/2 of 8.3 days. The patient was treated with oral ferrous sulfate.

Results

In this small group of patients there are 4 males and one female. The onset of the disease was during the second, third and fourth decades. The presenting symptoms of 4 patients were those of anemia and in the fifth patient it was hemoglobinuria. Upon further questioning 3 of the 4 patients with anemia also had hemoglobinuria intermittently. Besides pallor, the only other abnormality on physical examination was splenomegaly, present in 3 patients. Case 1 had no palpable spleen when examined 5 years later.

All patients had moderate to severe anemia when seen initially. Case 4 had a normal hemoglobin when examined 6 years after the onset of the disease. Case 2 was the only one who had an aplastic crisis documented by bone marrow studies. The peripheral blood showed macrocytosis and polychromatophilia in most instances. The white blood cell count was in the leukopenic range (below 5,000) in 4 patients and the polymorphonuclears ranged from 40 to 52%. The platelet count was decreased in 3 patients and low normal in a fourth one. The reticulocyte counts ranged from 14 to 46% in all cases. Two patients had clinical jaundice during the hemolytic crisis, but we could only document this in one patient. The BUN was normal in all the patients and only 3 patients had some degree of proteinuria.

The Coomb's tests, sickle cell preparation and presumptive test for osmotic fragility were normal in all the patients. The urinary sediment was of brownish color in all patients and the iron stain was strikingly positive. The bone marrow showed erythrocytic hyperplasia in all instances except Case 2 during the aplastic crisis. The iron stain of the bone marrow was originally increased in all cases except Case 4 in whom it was decreased. During our recent evaluation of 4 of the patients we found that two of those who originally were iron loaded now had no stainable iron in the bone marrow. Case 4 although in a partial remission still had no stainable iron either.

The neutrophil alkaline phosphatase score was 0 in 4 patients. Case 3 had a very high score when she had an infection, and at which time her granulocytes had marked toxic granulation. The erythrocyte acetylcholinesterase activity was done in 4 patients and was low in 3. Case 4 had a normal enzyme concentration. The Ham test and thrombin test were positive in all the patients. The sugar water test an autohemolysis test with and without glucose incubation were positive in the 4 patients in whom the tests were done.

The hemoglobin electrophoresis showed normal adult hemoglobin in 4 patients. Case 3 did not have it done. The serum iron was low in cases 1 and 5 when done recently. Case 2 and Case 4 had normal levels. The red blood cell survival was shortened in Case 1 and Case 5. Case 4 had a near normal survival.

In summary we have observed classical P.N.H. in five patients four of whom are alive 2 to 15 years after the onset of the disease. Our patients have only required blood transfusions and oral iron therapy. We have had no problem with thrombotic crisis or the hazards of surgery.

Pathophysiology of P.N.H.

The etiology of P.N.H. remains unknown. It is known that the defect lies in

the erythrocytes, the plasma being normal. It is thought that there is a defect in the stroma of the red cells but the nature of this defect has not been defined (10). It may be either structural or enzymatic. Abnormalities of their surface have been found by electronmicroscopy (11) and low or even absent acetylcholinesterase activity is known to occur in the abnormal erythrocytes (12).

The mechanism of their destruction by normal plasma in vivo and normal acidified serum in vitro has been a matter of controversy. Crosby in 1953 postulated the presence of two interdependent activators and two interdependent inhibitors (13). In each of these two groups there is a heat stable plus a heat labile component. Calcium and magnesium complete the hemolytic system. Any break in the balance normally present between the activators and the inhibitors will result in either augmented or decreased hemolysis of P.N.H. cells. According to Crosby thrombin by destroying the heat stable inhibitor breaks the balance in favor of the activators thus promoting increased activity of the hemolytic system. This is the basis for the Crosby thrombin test. More recently the importance of the properdin complex has gained support by the majority of those interested in the disease. It is thought that the properdin complex is adsorbed on the abnormal surface of the defective erythrocytes, this leading to their destruction by enzymatic activity. The complement complex apparently brings about the hemolysis (2).

Thrombocytopenia and leucopenia occur frequently in P.N.H. Abnormalities of platelets in this disease have not been confirmed although Crosby postulates that they are unusually susceptible to lysis by the P.N.H. plasma system. Abnormality of leucocytes in the form of a low or absent alkaline phosphatase activity is well documented (14, 15).

The clinical manifestations of PNH are those resulting from the erythrocytic abnormality. Perpetual intravascular hemolysis with hemolytic crises occurrying typically during sleep are characteristic. Hemoglobinemia, hemoglobinuria and hemosiderinuria occur on this basis. The depletion of the serum haptoglobins leads to the continuous presence of hemoglobin in the glomerular filtrate. The tubular cells are capable of reabsorbing all the hemoglobin presented by the glomerular filtration until the renal threshold is surpassed. Inside the tubular cell the hemoglobin molecule is split into the various components. The globin molecule is returned to the protein pool, the porphyrin moiety is returned to the blood stream either as bilirrubin or as hematin. The iron is returned to the bone marrow for new blood formation. When the renal threshold is overpassed, hemoglobinuria, siderosis of the kidney and hemosiderinuria occur. The kidney suffers little from the siderosis because the tubular cells are constantly replaced. The hemosiderinuria may protect the patient against transfusion siderosis, but if severe may lead to iron depletion (1).

In addition to the manifestations of intravascular hemolysis P.N.H. patients are unusually susceptible to infections especially to pneumonia and pyelonephritis and to thrombotic manifestations particularly of the portal and cerebral vascular beds. The increased susceptibility to infections is explained on the basis of the frequent presence of leukopenia. The thrombotic manifestations are thought to be due to a hypercoagulable state resulting from the release

of thromboplastic material derived from the hemolyzed red cells.

It must be stressed that in P.N.H. not all the cells are abnormal. The proportion of normal to abnormal cells vary in different patients, the severity of the disease depending on this ratio. As would be expected the higher the proportion of abnormal cells the more serious the manifestations of the disease (16).

Finally a few words about the possible relation between P.N.H. and bone marrow hypoplasia (17). In this disease, like in other hemolytic states bone marrow hypoplasia with resulting pancytopenia and reticulocytopenia may occur. This situation is frequently seen following infections especially those of viral etiology. It is a quite serious state of affairs as destruction of abnormal cells continues unchecked without replacement. If the marrow does not recover death will ensue. During this critical situation the liberal use of blood transfusions is mandatory.

In the recent literature the development of P.N.H. following unequivocal cases of aplastic anemia has been stressed. We know of one such case in Puerto Rico (18). What brings on the appearance of P.N.H. cells in such situation is speculative. According to Dacie a new clone of abnormal cells appears in damaged hypoplastic marrows as a result of abortive attempts at regeneration (2).

Management

There is no known curative treatment for paroxysmal nocturnal hemoglobinuria; therefore, care is directed towards the management of symptoms and complications. The main problems encountered are anemia, acute hemolytic crises, episodes of thrombosis and bleeding manifestations. These patients suffer from a chronic anemia and they adjust well to low hemoglobin levels. It is, therefore, unnecessary to attempt to maintain the hemoglobin wthin the normal range. A large number of plasma reactions are reported in P.N.H. and so when transfusions are required washed red blood cells should be used. Red blood cells triply washed with saline seem to be best. P.N.H. patients suffer from a constant hemosiderinuria and may become iron deficient. If the serum iron is low, iron should be given by mouth (0.3 gm/day) as hemolytic reactions have been reported with injectable iron (19). In our patients blood transfusions and iron therapy has been the only therapy required.

During acute hemolytic crisis washed red blood cell transfusions are also indicated. Hemolysis may be decreased temporarily by 6% Dextran (mol. weight 75,000) but the prolonged use of this agent is contraindicated because hemorrhagic manifestations may supervene (20). Hemolytic and aplastic crises are sometimes produced by infections and so antibiotics can be used. Folic acid deficiency and megaloblastosis has been reported, as in other hemolytic anemias, and folic acid therapy is then indicated (21).

Thrombosis is a frequent cause of death in these patients. Coagulation studies have shown variable results with several abnormalities reported (22). Anticoagulant treatment should be given with Dicumarol or one of its derivatives. Heparin is contraindicated in patients with P.N.H. because it accelerates the hemolysis (1). Some authors advocate the use of anticoagulants for

all acute hemolytic crisis. Bleeding manifestations are rare and when present are the result of thrombocytopenia.

The beneficial effect of corticosteroids and ACTH has not been established except for rare patients with a positive Coomb's test (1). No definite beneficial effects have been reported with splenectomy. Androgens have been used successfully in some patients and it appears that besides stimulating the marow it may also diminish the hemolytic process (22, 23).

Summary

Paroxysmal nocturnal hemoglobinuria is a chronic acquired hemolytic anemia of unknown etiology. The disease is characterized by intravascular hemolysis, hemoglobinemia, paroxysmal hemoglobinuria and hemosiderinuria. In the five patients that we studied anemia was the presenting symptom, but upon questioning hemoglobinuria was also present. We found leukopenia, thrombocytopenia and splenomegaly in some cases.

The laboratory studies revealed positive Ham test, thrombin test and sugar water test. The urinary hemosiderin was positive in all cases. The bone marrow was classical of hemolysis in all patients except in one instance when a patient had an aplastic crisis. The bone marrow iron was increased originally in 4 of the 5 patients but on subsequent examinations 3 patiens were found with no storage iron. Two patients had low serum iron and 2 others were normal.

One of our patients died of infection. In the other 4 patients we have observed no other complications. Therapy has consisted of saline washed packed red cells for the anemia and oral iron for the iron deficiency.

Resumen

La hemoglobinuria nocturna paroxística es una anemia hemolítica crónica y adquirida de origen desconocido. La enfermedad se caracteriza por hemólisis intravascular, hemoglobinemia, hemoglobinuria paroxística y hemosiderinuria. En los cinco pacientes estudiados la anemia fue el síntoma principal, pero la hemoglobinuria también estaba presente. Frecuentemente se encontró leucopenia, trombocitopenia y esplenomegalia.

Los estudios de laboratorio revelaron que las pruebas de Ham, trombina y "agua de azúcar" fueron positivas en los casos estudiados. La hemosiderina en la orina también fue positiva en todos los casos. La médula ósea demostró cambios de hemólisis en todos los pacientes, excepto en un paciente cuando tuvo una crisis aplástica. La tinción de hierro en la médula ósea demostró aumento en 4 pacientes originalmente, pero con el transcurso del tiempo 3 de los pacientes demostraron ausencia de hierro. Dos pacientes tuvieron hierro sérico bajo y dos fueron normales.

Uno de nuestros pacientes murió de infección. En los otros 4 pacientes no hemos tenido complicaciones serias. La terapia ha consistido de transfusiones de células rojas lavadas con salina y hierro oral en los pacientes con deficiencia.

Acknowledgement

The authors wish to express their gratitude to Dr. Thomas Sheehy and Dr. José

TABLE I: CLINICAL ASPECTS

Case No.	Sex	Age (Yrs.)	Duration of Symptoms (Months)	Chief Complaint	Splenomegaly
1	M	44	21	Hemoglobinuria	Yes
2	M	62	57	Anemia	Yes
3	F	46	7	Anemia	Yes
4	M	28	36	Anemia	No
5	M	44	7	Anemia	No

TABLE II: ROUTINE LABORATORY FINDINGS

Case No.	Hemoglobin Gms./100 ml.	WBC	Reticulocyte Count	Platelets	Total Bilirubin Mg./100 ml.	BUN Mg/100 ml.
1	4.6	1,450	46.2%	60,000	—0.4	13
2	6.8	4,200	15 %	38,000	1.9	15
3	2.9	2,650	14 %	10,000	- -	8
4	6.0	3,250	15.8%	140,000	0.3	12
5	8.5	5,650	45 %	208,000	0.7	14

TABLE III: SPECIAL STUDIES

Case No.	Ham Test	Thrombin Test	"Sugar water" Test	Erythrocyte Cholinesterase	Urinary Hemosiderin
1	Positive	Positive	Positive	Low	Positive
2	Positive	Positive	Positive	Very low	Positive
3	Positive	Positive	———	———	Positive
4	Positive	Positive	Positive	Normal	Positive
5	Positive	Positive	Positive	Low	Positive

TABLE IV: SPECIAL STUDIES

Case No.	Coomb's Test	Neuthrophil Alkaline Phosphatase	Serum Iron mcgm./100 ml.	Bone marrow iron Initially	— Recently
1	Negative	0	15	Increased	None
2	Negative	0	120	Increased	Increased
3	Negative	366	—	Increased	———
4	Negative	0	80	Low	None
5	Negative	0	30	—	None

Soler for the evaluation of the first two patients. We also want to thank Dr. Sigfredo Lazarini and Dr. Zenón Rivera-Biascoechea for referring their patients and Dr. Ferdinand Ruiz for following one patient. We are also grateful to doctor Carlos Náter, Raúl Bacó and José Corcino, who are responsible for some of the evaluations of these patients.

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LA MEDICION DE PBI-131 EN LA DISFUCION TIROIDEA

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Siguiendo con el plan de analizar los resultados de las pruebas de función tiroidea que se realizan en nuestro medio, específicamente en el Laboratorio de la División de Aplicaciones Clínicas del Centro Nuclear de Puerto Rico y alentados por la valoración regional o geográfica peculiar de los resultados obtenidos en la evaluación de la captación de yodo a las 24 horas publicado en 1964 (1) y confirmados con trabajos posteriores (2), hemos reunidos los valores encontrados en las determinaciones de la relación de conversión de iodo proteico y niveles de iodo proteico plasmático (en adelante se denominarán por el símbolo de PBI-CR y PBI-PL, respectivamente), con el objeto de hacer el análisis estadístico de los mismos.

Recordamos que cada una de estas pruebas estudia uno de los pasos del metabolismo tiroideo y que un solo resultado carece de valor diagnóstico siendo, como siempre, importante la realización de varias pruebas para poder sacar conclusiones definitivas. Un solo resultado puede llevarnos, aún realizado en las mejores condiciones, a conclusiones erróneas.

Desde los históricos trabajos de Hertz (3) y de Hamilton (4) hace ya casi 30 años, con los que se introdujo el yodo radioactivo en el estudio de la función tiroidea, los resultados obtenidos y el valor de su interpretación ha estado sometido a una larga controversia pese a que, en el mundo entero, han sido hace tiempo admitidas esas pruebas en la rutina médica diaria. El mejoramiento constante de las técnicas y del instrumental disponible, ha ido haciendo más accesibles las mediciones en sangre iniciadas por Chaikoff (5), Clark (6), Stone (7), Silver (8, 9), y otros. Esta evolución fue llevando también un lado, al ajuste de los resultados considerados como normales y a la observación de los factores que inciden sobre los mismos (10, 11, 12, 13, 14), y a la limitación del valor de éstos a los casos en que son realmente útiles (15, 16, 17). Después de todo ello, aún reconociendo que ya se ha escrito mucho sobre ésto, pero pensando que cada región, o mejor, cada grupo de trabajo debe fijar sus valores normales para cada técnica y analizar la importancia de la desviación de esos valores en los diferentes estados patológicos, es que se decide publicar estos resultados.

De la División de Aplicaciones Clínicas del Centro Nuclear de Puerto Rico.

Material

Se han analizado algo más de 460 casos provenientes principalmente de los Hospitales Universitario y Municipal de Río Piedras referidos a la

División de Aplicaciones Clínicas del Centro Nuclear de Puerto Rico para la realización de pruebas de función tiroidea con I^{131}. Puede considerarse ese grupo como exponente de la población de una gran parte de la isla ya que estos hospitales, y especialmente el Universitario, reciben pacientes enviados de los diferentes Centros de Asistencia de la parte Nordeste del país. Se seleccionaron aquellos a los que, además de medirse la captación glandular se le hubiera determinado la relación de conversión de yodo plasmático y el valor de sus niveles de yodo radioactivo proteico a las 24 y 48 horas. Del estudio de todos ellos se seleccionaron 292 cuyos cuadros clínicos de función tiroidea se consideraron categóricos y se agruparon en la siguiente forma: Eutiroideos 201, Hipotiroideos 26, Hipertiroideos 65. En el primer grupo se separaron 42 casos que teniendo una función normal, tenían una glándula agrandada más de dos veces lo normal y se analizaron aparte, quedando el grupo de los eutiroideos reducidos a 159 pacientes clínicamente normofuncionantes y con una glándula normal o ligeramente aumentada de tamaño.

El criterio de selección de cada grupo fue eminentemente el estado clínico en el momento de la prueba y su posterior evolución. Apoyado, en los casos necesarios, en la consideración del dosaje de colesterol, y los valores de captación a las 24 horas según los límites fijados para este laboratorio (1). Se excluyeron pacientes que ya habían sido tratados por disfunción tiroidea por la discrepancia que se encuentra en los resultados de los mismos (18). En el conjunto hay 15% de varones y 85% de mujeres, con una variación bien amplia en las edades pero con predominancia entre 20 y 40 años que es en general la relación con que se presentan a estudio tiroideo los pacientes. No se tuvo en cuenta la temperatura ambiente ya que su influencia está en controversia (19, 20), y que si la tuviera no lo sería sobre PBI sino sobre la captación (13).

Todos los pacientes fueron interrogados previamente para descartar la influencia de yodo exógeno o cualquier otra medicación o estado patológico no tiroideo que pudiera falsear los resultados, según es de rutina en estos casos.

Las mediciones se efectuaron con equipos con cristal de pozo de yoduro de sodio activado con talio de 2" de diámetro con escalímetros decimales y un blindaje suficiente para contar una actividad de fondo de 300 a 400 cuentas por minuto.

Método

Se administró a los pacientes por vía oral en cápsulas precalibradas una dosis que varió entre 80 y 100 uc. No se hizo diferencia entre que el paciente estuviera o no en ayunas ya que se considera que en pruebas que se realizan a las 24 o más horas ese factor no incide en forma notable.

A las 24 y 48 horas se extrajo sangre con heparina para efectuar las mediciones dentro de las 48 horas de esa extracción. Al mismo tiempo, a esos pacientes, se les midió captación tiroidea de 24 y 48 horas por la técnica de Brucer (21). Se efectuó cálculo de la relación de conversión según Clark (6) y el nivel de yodo en proteínas de plasma según Stone Freedberg (7) y Silver (9), utilizando resina Amberlita IRA 400 para la separación del yodo inorgánico del fijado a las proteínas (22, 23, 24). Se midieron 3cc de cada plasma antes y después de ser filtrados por la resina hallándose la relación entre ambos.

En el caso del nivel plasmático se relacionó la actividad del plasma filtrado con un testigo conocido (solución de I-131) y se expresó en por ciento de la dosis administrada por litro de plasma.

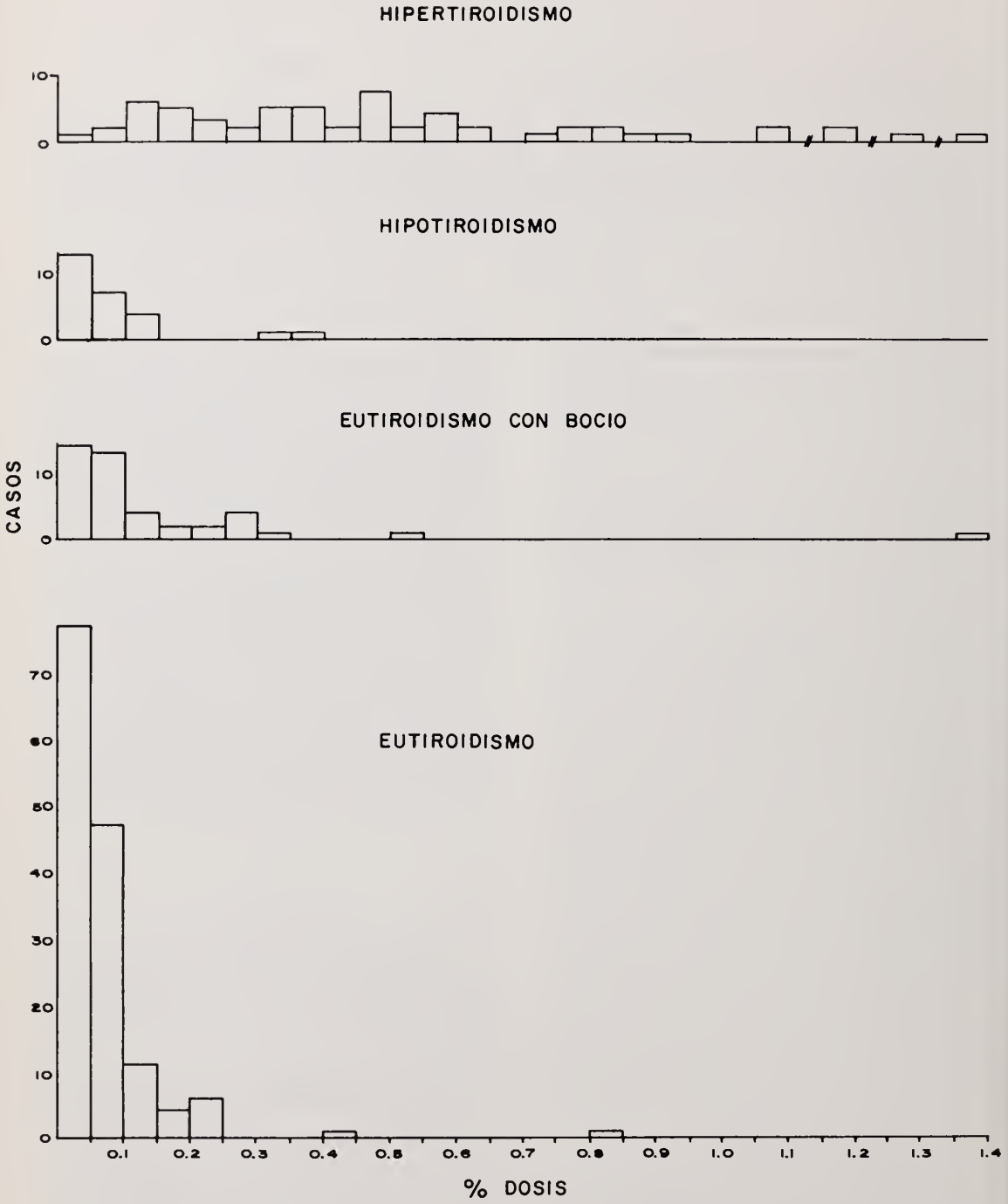
En todos los casos la muestra se midió el tiempo necesario para obtener un mínimo de 10,000 cpm y luego se efectuó una nueva medición de 1 minuto para control. Se utilizó para el estudio la primera de dichas mediciones. Se realizó luego el análisis estadístico de esos resultados.

Resultados

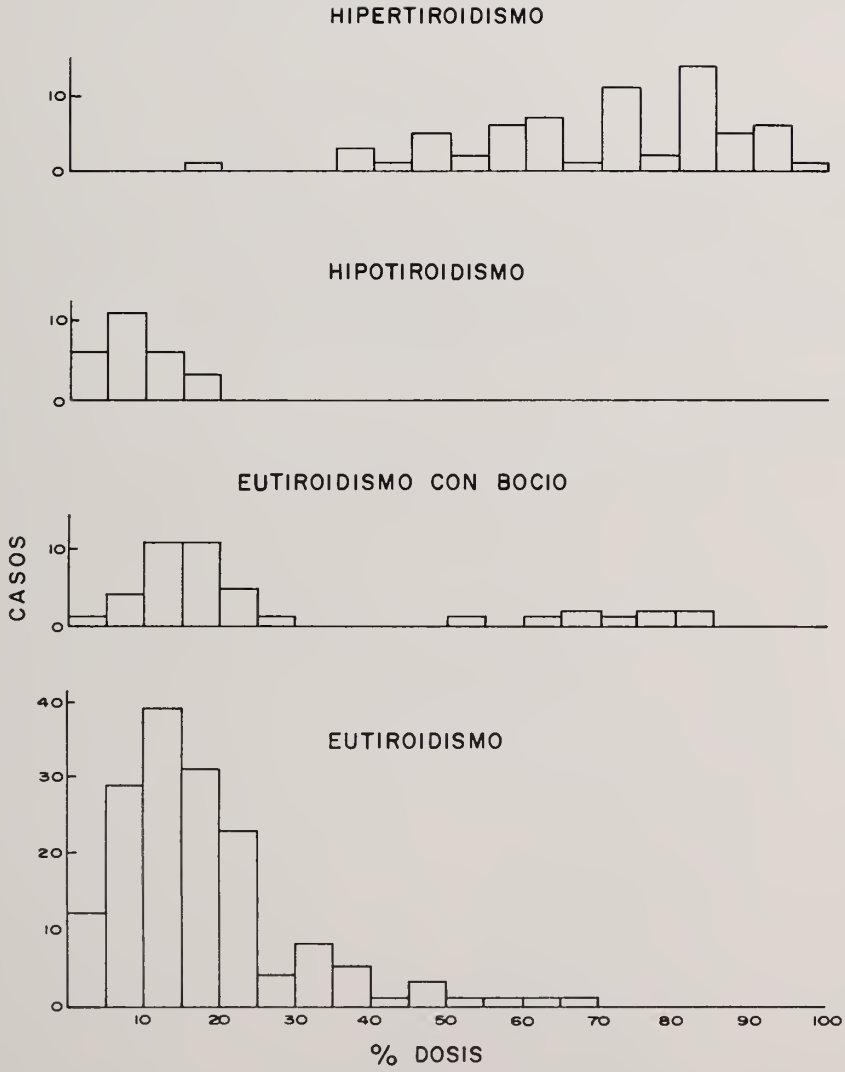
Dicho estudio estadístico de los resultados, correspondientes a los 292 pacientes seleccionados, se muestra en los cuadros I y II.

Hecho el estudio del valor de las diferencias, matemáticamente consideradas, se obtuvo que:

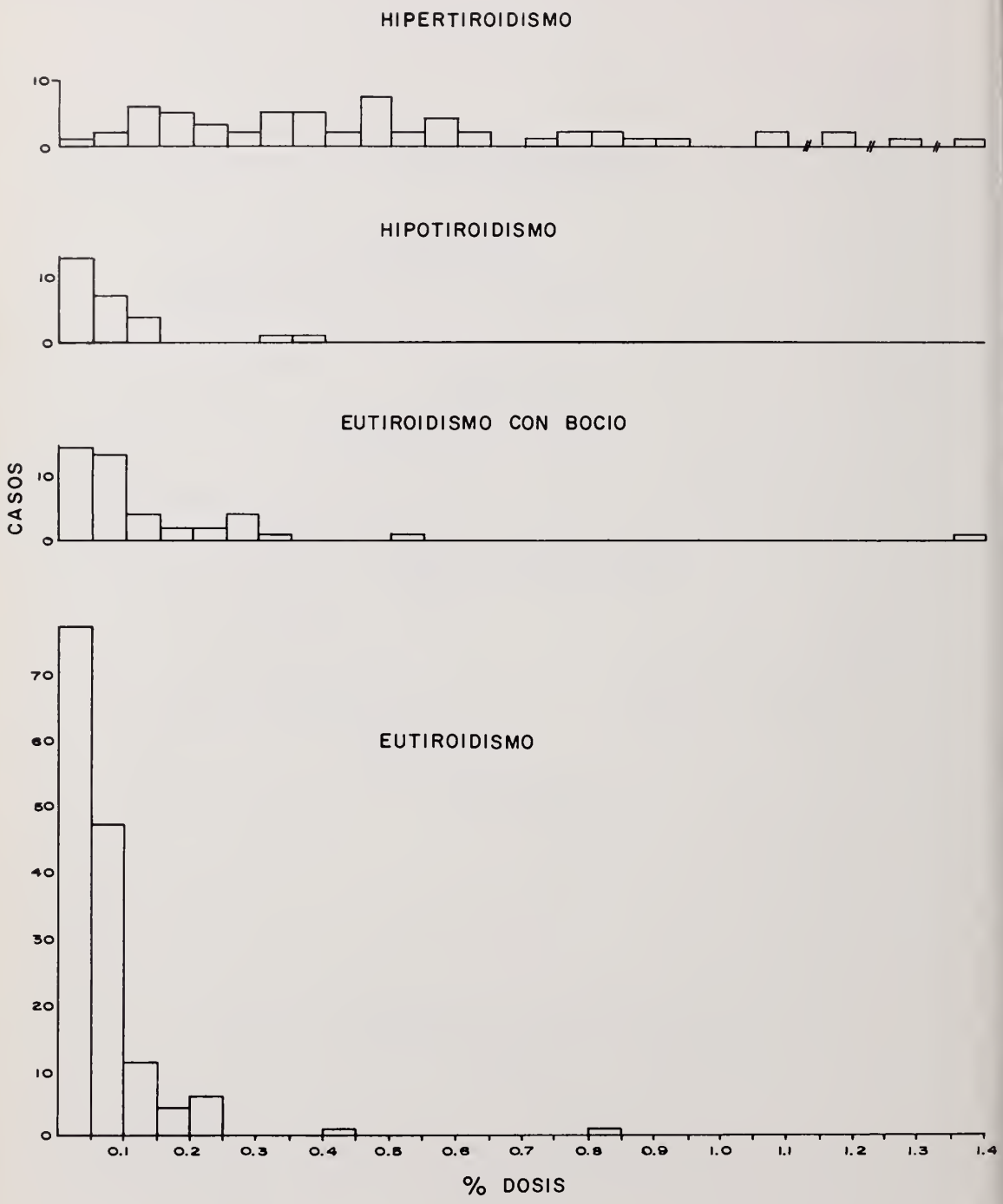
a) Los valores obtenidos para todas las pruebas incluyendo captación de yodo a las 24 y 48 horas en los eutiroideos con bocio son significativamente mayores que en los



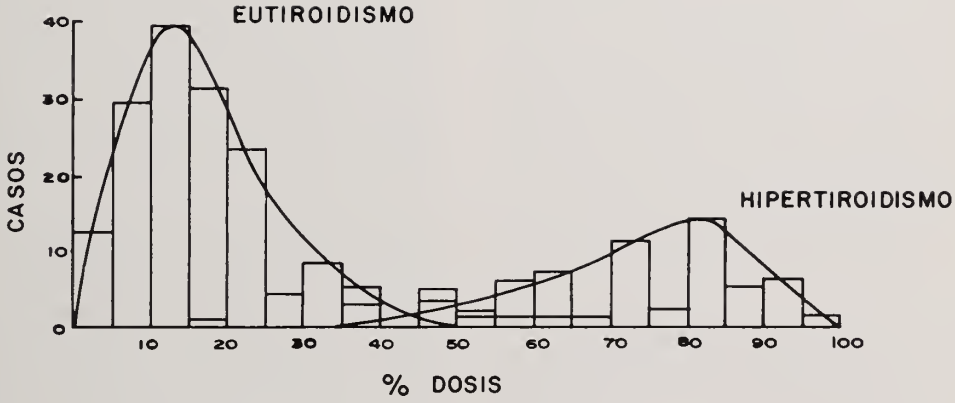
Graf. 1: Razón de conversión.



Graf. 2: Nivel plasmático de 24 horas.



Graf. 3: Nivel plasmático de 48 horas.



Graf. 4: Razón de conversión.

sin bocio (p 0.01 excepto captación 48 horas en que p 0.05).

b) En los eutiroideos los valores de PBI PL de 24 y 48 horas no tiene diferencia significativa, siendo en cambio la captación de 48 horas mayor que la de 24 horas (p 0.01).

c) En los hipertiroideos la diferencia entre las pruebas de 24 y 48 horas, para el nivel plasmático y para la captación, no es significativa.

d) En los bocios tampoco hay cambio en esos valores de las 24 a las 48 horas.

La distribución de esos resultados está representada en los gráficos 1, 2, 3.

Discusión

Con respecto a los resultados obtenidos en el PBI -CR se puede decir, si no se consideran los resultados de los pacientes bociosos, que ellos están agrupados en forma bien definida, habiendo una buena separación entre el límite superior de los normales con respecto al límite inferior de los hipertiroideos. Entre ellos hay una superposición de 8.1% de pacientes eutiroideos sobre el nivel superior de ese grupo y 6.1% de los hipertiroideos bajo el nivel inferior para pacientes hipertiroideos, lo que puede considerarse una buena definición para esta prueba (gráfico 4). Atendiendo a la distribución de esos casos, en los gráficos puede observarse la relativa simetría de los mismos, hecho que está de acuerdo a los valores aproximados de media y mediana en ambos casos.

Ninguna de esas observaciones tiene similares al considerarse eutiroideos e hipotiroideos, donde la superposición es casi total.

Este análisis está de acuerdo con lo esperado, teniendo en cuenta los trabajos anteriores presentados sobre la prueba, que ya era recomendada como muy buena por Riggs (25) en el 1952, y es dada como útil especialmente para diagnosticar hipertiroidismo (12, 17, 26).

En el grupo de los pacientes con bocio eufuncionantes la dispersión es muy grande, parecería insinuarse una división en dos grupos, uno que va de 5 a 30% y el otro de 60 a 85%, aunque para hacer subdivisiones la cantidad de casos de que se dispone es muy pequeña. Sin embargo, el promedio general de resultados es significativamente mayor que en los eutiroideos.

Los valores de PBI-PL a las 24 y 48 horas pueden ser analizados en conjunto ya que las dos series presentan características muy similares. Aunque en ellos los valores correspondiente a pacientes normales están concentrados en una zona y muestran límites bien definidos, los que pertenecen a hipo e hipertiroideos están indefinidos y dispersos y es imposible demarcar puntos de los cuales partir. La superposición entre hipo y eutiroideo está próxima al 100%. En el otro extremo los normales penetran en zona de los hipertiroideos en el 100% de los casos, mientras a la inversa, para los hipertiroideos esa superposición en la zona de valores normales es de 47.5 a las 24 horas y 28.3 a las 48 horas. Estos últimos hallazgos no están de acuerdo con la opinión de la generalidad de los autores que, aunque coinciden en que el PBI-PL no tiene valor para diferenciar eutiroidismo del hipotiroidismo, dicen es, en cambio, muy útil para hacer esa diferencia entre eutiroideos e hipertiroideos (16, 27, 28, 29, 30).

En los pacientes bociosos los valores de niveles plasmáticos están en parte dentro de la zona normal, pero estos resultados se extienden hacia arriba lo suficiente como para dar tanto a las 24 como a las 48 horas promedios significativamente mayores que en los normales hechos que coincide con los resultados obtenidos en algunas zonas endémicas donde, los bocios grados II y III de la escala de los OMS presentan valores de PBI-PL altos también (31).

Sin embargo, si observamos la serie normal se ve que solamente tres casos tienen, tanto a las 24 como a las 48 horas, niveles plasmáticos mayores al límite superior para eutiroidismo (promedio + 2 desvíos standard, 0.26) los que significan 2% de error en ese diagnóstico.

Esta observación se mantiene aún en los pacientes con bocio grande donde el error es de 7.5 y 6% a las 24 y 48 horas respectivamente. Esto hace la prueba útil para confirmar hipertiroidismo en el caso de la obtención de un resultado elevado.

Por consiguiente ninguna de las pruebas estudiadas tiene valor para el diagnóstico del hipotiroidismo, para el cual hay que continuar con el dosaje del PBI^{127} (32, 12) aún teniendo en cuenta todas las dificultades técnicas que presenta Enriori (33). Para el diagnóstico entre eu e hipertiroidismo el cálculo de la relación de conversión tiene valor si consideramos a 40% como límite superior en cambio, y contrariamente a lo expuesto por numerosos autores en otros lugares, el nivel plasmático de proteínas marcadas con I^{131} a las 24 ó 48 horas, no presenta límite inferior definido en caso de hiperfunción. La relación entre este hecho de observación y el presentado anteriormente, del promedio bajo de captación tiroidea de yodo (1) en la población de Puerto Rico, podrían estar relacionados si es que aceptamos como causa de la captación baja a un cierto grado de saturación yodada de dicha población. Si las causas fueran esas, podría explicarse como paralelo, esos valores bajos de PBI-PL aún en casos de hiperfunción glandular.

Resumen y Conclusiones

Se analizaron valores obtenidos en la determinación de relación de conversión y niveles plasmáticos con I^{131} en el laboratorio de Aplicaciones Clínicas del Centro Nuclear de Puerto Rico con el objeto de fijar valores normales locales para esas pruebas. Se realizó el estudio de 292 pacientes seleccionados por su diagnóstico indubitable respecto a función tiroidea, agrupados de la siguiente forma: eutiroideos, 159; eutiroideos con bocio dos o más veces el tamaño normal, 42; hipotiroideos, 26; hipertiroideos, 65.

Se analizaron estadísticamente los resultados obtenidos en esos pacientes para relación de conversión del yodo plasmático con I^{131} a las 24 horas y niveles plasmáticos de yodo proteico (I^{131}) a las 24 y 48 horas.

De ese análisis se obtuvieron las siguientes conclusiones:

1. La relación de conversión no es útil para el diagnóstico de hipotiroidismo, pero sí lo es para el de hipertiroidismo, considerándose como valor límite entre eu e hiperfunción el de 40%. Esa utilidad disminuye cuando el paciente presenta un bocio más de 2 veces el tamaño normal.

2. Los niveles plasmáticos de yodo proteico a las 24 ó 48 horas no permiten diag-

nosticar hipotiroidismo pero sí hiperfunción si su valor está por encima de 0.26% D/L. En cambio no descarta esa posibilidad si su resultado es menor, ya que existe un gran porcentaje (47.5% para la prueba a las 24 horas y 28.3% a las 48 horas) de hipertiroideos que se encuentran por debajo de esa cifra.

Se sugiere que esos valores bajos hallados en esta prueba puedan estar relacionados con un cierto grado de saturación yodada de los habitantes de esta zona que sería también responsable de la baja captación de 24 horas por la glándula (20.0 + 9.3%).

Este interrogante será objeto de un futuro estudio, el cual esperamos, nos permita entender mejor este aspecto del metabolismo del yodo en nuestros pacientes y la aparente peculiaridad geográfica de los valores discutidos.

Summary and Conclusions

The values obtained at the Clinical Applications Division of the Puerto Rico Nuclear Center in the determination of radioiodine blood hormone levels by the techniques known as protein bound conversion ratio and protein bound (I^{131} plasma level were analyzed to define the limits of thyroid function by these tests in our laboratory and to learn what values of normal and abnormal thyroid functions are applicable to our patient population.

The study was carried out on 292 patients who presented unequivocal clear cut pictures of thyroid disorder or eufunction. The group consisted of 159 euthyroids, 42 euthyroids with goiters twice normal size or larger, 26 hypothyroids and 65 hyperthyroids.

The results of the 24 hour protein bound conversion ratio and the 24 hour protein bound plasma levels observed in these patients were statistically analyzed. The evidence obtained from this analysis permits us to draw the following conclusions:

1. The results obtained by the protein bound conversion ratio is worthless for the diagnosis of hypothyroidism, but is of great value in differentiating between hyperthyroidism and euthyroidism; the upper limit of "normal" thyroid function for patients may be set at 40% per 24 hours. When the patient has a goiter twice than normal or larger, the usefulness of this test diminishes considerably.

2. The results observed with protein bound I^{131} plasma levels at 24 and 48 hours are also non diagnostic for hypothyroidism but are diagnostic of hyperthyroidism if the values are above 0.26% administered dose per liter. A level below 0.26% dose/liter of plasma does not rule out the diagnosis of hyperthyroidism since 47.5% of the values at 24 hours, and 28.3% at 48 hours belong to hyperthyroid patients who have values below that level. (0.26% dose/liter upper limit of normal.)

It is speculated that the low values observed in this test in hyperthyroid patients may be related to some degree of iodide saturation of the people inhabitating this area which would also be responsible for the relatively low 24 hour I^{131} thyroid uptake. (20.0 + 9.3% average value and standard deviation for euthyroid patients in this study.)

This unanswered problem will be studied further and we hope its study may help us understand and better this aspect of the

CUADRO I: ACUMULACION DE IODO 131 EN GLANDULA E INCORPORACION A HORMONA

	Captación * 24 horas	Captación 48 horas	Núm.	Razon de Conversión ** Prom. ±	Rango	Mediana
Eutiroidismo	20.0 ± 9.3	23.2 ± 8.3	159	17.4 ± 11.8	1.5 - 65.5	14.6
Bocio Eut.	28.2 ± 17.9	28.2 ± 16.9	42	27.4 ± 24.1	4.1 - 81.1	17.1
Hipotiroidismo	7.7 ± 6.4	8.2 ± 7.3	26	9.1 ± 4.8	2.4 - 19.2	9.0
Hipertiroidismo	59.8 ± 9.5	56.9 ± 9.7	65	70.4 ± 17.1	19.0 - 97.0	73.2

* Porciento dosis fijada por la glándula a la hora indicada.

** Porciento yodo I 131 fijo en proteínas comparado con el total en sangre.

CUADRO II: NIVELES PLASMATICOS DE I-131 PROTEICO EN % DOSIS POR LITRO DE PLASMA

	PL 24 Horas Núm.	P. ±	Rango	Med.	PL 48 Horas Núm.	P. ±	Rango	Mediana
Eutiroidismo	155	.08 ± .09	.01 - .80	.07	148	.075 ± .09	.01 - .85	.05
Bocio Eut.	40	.14 ± .06	.03 - 1.20	.085	42	.15 ± .07	.01 - 1.40	.095
Hipotiroidismo	26	.085 ± .06	.01 - .36	.08	26	.08 ± .08	.02 - .32	.055
Hipertiroidismo	61	.41 ± .47	.03 - 2.20	.28	60	.58 ± .61	.04 - 3.40	.45

metabolism of iodine in our patients and the apparent geographical pattern of the values discussed here.

Reconocimiento

Agradecemos a los Profesionales de estos Centros y de otros de la Isla, especialmente de sus Servicios de Endocrinología, y hacemos destacar la colaboración prestada por los mismos al referir sus pacientes y facilitar los datos clínicos de los mismos.

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PREVALENCE OF DIABETES IN A SAMPLE OF THE ADULT POPULATION IN PUERTO RICO

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To date, there has not been published any population-based estimates of diabetes mellitus prevalence for Puerto Rico. Any such study will encounter some very definite problems because though blood tests are for more sensitive than urine, the age, sex, time of testing, the size and effect of the glucose load or glucose content of the diet, the use of venous versus capillary blood, and the blood analytic method used will all affect test results (1, 2, 3).

We have been interested for some time in making the public conscious of diabetes, in finding some preliminary data about response rate and how the general public would respond to this type of program. To get some experience and find out what particular problems would come up we decided to subject to this program the female employees of the Puerto Rico Water Resources Authority located in Santurce. We found that the management and the members of the staff were most cooperative and soon our project was started.

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Materials and Methods

As a preliminary step, all female members of the company were assembled in the Puerto Rico Water Resources Auditorium and weve given talk on diabetes and why they should be interested in finding out whether they were diabetic or not. All of them were given a questionnaire, which was the basis for their being classified as "normals" or "probably abnormal".

Patients were classified as normals if they had no family history of diabetes, had never given birth to a baby 10 pounds or more in weight, had no history of thyroid disease, were not taking any medicines known to alter the glucose tolerance (Enovid, thiazides, cortisone), were not pregnant, were not following reducing diets which could cause a starvation type of glucose tolerance curve, and had no intercurrent illness.

Overweight patients were included among the normals unless they had to be excluded because of one of the above stated criteria.

All patients classified as "normals" were given an appointment for a glucose tolerance test. They were placed on a 300 gm carbohydrate diet for 3 days prior to the test.

The glucose tolerance test were performed in the fasting state. A sample for fasting blood sugar was taken and glucose was given orally in a dosage of 30 gms/square meter of body surface. The body surface was calculated from the height and weight using the Dubois Nomogram criteria (4). Samples for blood sugar were taken one, two and three hours after the ingestion of glucose. The glucose tolerance test was considered to be diabetic when the sum of the fasting, one, two and three hours values was 500 mgs% or more (University Group Diabetes Program criteria) (5).

The employees that could not be classified as normals according to the criteria already stated were classified as probably abnormal. They were given while fasting 30 gms of glucose/square meter of body surface and a sample for blood sugar was taken one hour afterwards. If the blood sugar was 130 mgs% or more, the employee was recalled for a glucose tolerance test. The patients voided prior to receiving the glucose. A urine sample was taken at the time the one hour post-prandial blood sugar was taken and was tested for the presence of reducing substances with Clinitest.

Blood samples were taken in #3200 PS Vacutainer tubes containing 20 mgs. of sodium fluoride and 20 mgs. of potassium oxalate for about 10 milliters blood. Blood samples were run the same day Laboratories). This is a modification of the method proposed by W. S. Hoffman. (6).

Results

The population studied was made up of 125 female employees of the Puerto Rico Water Resources Authority. These were mostly secretaries. The age distribution of those tested is shown in Table I.

Seventeen employees refused to be tested at all. This gives a non-response rate of 14%. One of the employees that refused was a known case of diabetes. This patient's record was reviewed and her diabetes was confirmed. Thirty six patients were classified as normals; of these, thirty five had a normal glucose tolerance curve. One patient, an overweight 54 years old lady, had an abnormal curve.

Seventy two employees were classified as probably abnormal. The reasons for this are shown in Table II. They were subjected to a one hour post-glucose load blood sugar. Four had a positive screening test and were subsequently subjected to a glucose tolerance test. Out of these one was found to be positive. All urine samples were negative.

TABLE I: AGE - DISTRIBUTION OF SUBJECTS TESTED

Age (years)	No.
20 - 29	60
30 - 39	36
40 - 49	9
50 - 59	3
Total	108

TABLE II: REASONS WHY CLASSIFIED AS PROBABLY ABNORMAL

Reason	No. of Patients
Unhealthy	8
Intercurrent infection	4
Treatment with blood sugar altering drugs	27
Diet	0
Liver disease	2
Thyroid disease	3
Large baby	1
Family history of diabetes	47
Pregnant	4
Treatment with Enovid	12

Total adds up to more than seventy two because some patients were clasified as probbaly abnormal on the basis of multiple reasons.

In summary, out of 108 patients tested, three were found to be diabetics, which gives a prevalence of 2.7%. Out of these, 0.92% corresponds to known diabetics, 1.8% to unknown cases. Results obtained are shown in Table III.

TABLE III: SUMMARY

Group		Diabetics found
Total employees	125	
Tested	108	2 (unknown)
Normal	36	1
Probably abnormal	72	1
Refused	17	1 (known)

Discussion

No population-based studies of prevalence of diabetes have been published for Puerto Rico. The Department of Health has a screening program in which they reported a prevalence of 7.6% for 1959, 12.1% for 1960, 6.1% for 1961 and 9.6% for 1962 (7). These figures are higher than those reported by investigators in other areas except perhaps Winterbotham in Mabuiag Island (8) and Miller in the Pima indians (9). The group studied by the Department of Health consists of persons who voluntarily go for testing and may be weighed in favor of known diabetics and their relatives who are highly motivated. However, because these are the only available figures, we are quoting them.

The prevalence we found in this group is similar to that found by Ganguly et al in India (10) but twice that found by Wilkerson and Krall in Massachusetts (11).

The improvement of the medical care in Puerto Rico has increased the life span. In 1940 the average span of life in Puerto Rico was 46 years while in 1962 it was 69 years. Diabetes prevalence rates increase rapidly with age having a peak in the 6th to 8th decade of life. This factor and that of intermarriage could possibly account for a higher prevalence of diabetes in Puerto Rico. This question remains unanswered.

The urine test once more proved to be of no value as a screening test for diabetes, as pointed out by Sharp (12) and by Parker (13).

Usually the glucose tolerance test used for diagnosis of diabetes is that developed by Conn and Fajans (14). However, the amount of glucose used will produce nausea in a large number of subjects. This tolerance also gives the same challenge to patients underweight, overweight or of normal weight. We followed the recommendations given at the Conference on Methodological Approaches to Population Studies on Diabetes held in Bethesda, Maryland, Oct. 1-2, 1964. Here it was recommended that a challenge based on surface area be given. Following these recommendations we have used the criteria used by the University Group Diabetes Program (5) which uses 30 gm/square meter of body surface. By adding the fasting, one hour, two hour and three hour values in a group of symptomatic diabetes and then doing the same in the general population and by using as a cut off point area where there was overlapping, this group came to the conclusion that from 500 mg% up they would have the diabetics. Because the zone of overlap was excluded, with this criterion we are probably underdiagnosing diabetes. We did this in order to be sure that those we labeled diabetic would be regarded as such by most clinical investigators.

We want to point out that we can not in any way use these results to speak about the prevalence of diabetes in Puerto Rico, but we thought that groups interested in this problem would like to know about this small project, which could help in planning others.

Summary

No population-based studies for the prevalence of Diabetes Mellitus have been published for Puerto Rico. We have studied the female employees of a public corporation. Results are summarized in Table III. This gives a prevalence of 2.7% (known and unknown). These results should not be used in reference to the prevalence of diabetes in Puerto Rico.

Resumen

Hasta el presente no hay cifras oficiales sobre la prevalencia de diabetes en Puerto Rico basadas en pruebas de sangre hechas a una muestra representativa de la población. Este artículo ofrece los resultados encontrados en los empleados de una corporación pública. Estos resultados no deben usarse como base para hablar sobre la prevalencia de Diabetes en Puerto Rico.

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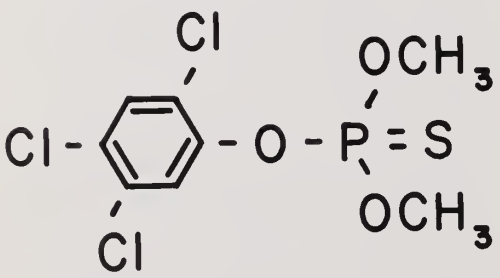
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EVALUATION OF RONNEL IN SCHISTOSOMIASIS MANSONI

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Ronnel (Pitman-Moore Division of Dow Chemical Co.) is an organic phosphorus compound with the chemical formula: O, O-dimethyl 0-2, 4, 5-trichlorophenyl phosphorothiate. Its structural formula is shown in Fig. 1.



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It is an inhibitor of cholinesterase and upon single and repeated oral feedings affects predominantly the pseudo-esterase of the plasma rather than the true acetylcholinesterase (1). It is rapidly absorbed by the gastro-intestinal tract. The rate of excretion varies in different species but it is excreted primarily in the urine in the form of degradation products.

Ronnel has a low acute oral toxicity. Its LD_{50} (mg/kg of body weight) is 1740 in rats and 2140 in mice. Lower dosages cause only transient or no effect at all. Excessive dosages of Ronnel result in symptoms characteristic of a cholinergic nature commonly associated with organic phosphate compounds (2). The chronic oral toxicity of Ronnel is low. Rats maintained for two years on diets administering 50, 15, 5, 1.5 or 0.5 mg of Ronnel per Kg of body weight per day appeared normal in general appearance and behavior (2).

Former code names of Ronnel were Dow ET - 57 and ET - 14. It is available commercially for veterinarian use under the trade names of Ectoral, Trolene and Korlan which are effective as a systemic insecticide for cattle grub control and treatment of ectoparasites in dogs and other animals (2).

In 1947, the organic phosphates were introduced as insecticides by German chemists who developed them during World War II while working with poisonous "nerve" gases. The acute toxicity of these compounds is a result of their ability to inactivate cholinesterase by phosphorylation of the enzyme's active center. From the physiological viewpoint, this produces alterations in the neural activity at three sites: 1) stimulation of postganglionic cholinergic nerves (muscarinic action) ; 2) stimulation of preganglionic cholinergic and somatic motor nerves (nicotinic actions) ; 3) central nervous system stimulation and depression.

The clinical picture seen in a patient with organic phosphate intoxication results from a combination of abnormal muscarinic, nicotinic, and central nervous system effects. There is nausea, vomiting, hyperhidrosis, excessive salivation, miosis, increased bronchial secretions and constriction, diarrhea and loss of bowel and bladder control. The anoxia due to retained secretions and pulmonary edema results in cyanosis and eventual death from asphyxia (3).

In Puerto Rico the advent of organic phosphate insecticides posed a new and tragic problem: that of intentional ingestion of these preparations in suicide attempts. In 1963 Girod (4) reported a series of ten cases of Parathion poisoning seen at the University Hospital in San Juan, Puerto Rico in a period of eight years (January 1955 to October 1963). In nine of the ten cases the persons took the pesticide orally with the intention of commiting suicide. Despite the fact that the majority of patients were acutely ill on admission and that most of them had ingested large amounts of Parathion, all survived because of promptness in the initiation of atropine therapy and supportive measures. The newer preparations derived from hydroxamic acids and the oximes such as 2-PAM (2-Pyridine aldoxine methiodide) were not used in these cases because they were not available (4).

Interest in the use of organo-phosphorus compounds as antihelminthics was generated by our group upon learning of the work of the Belgian investigators Cerf, Lebrun, and Dierick, who during the years of 1958 to 1960 conducted a study in Leopoldville, Belgian Congo with the phosphoric ester known as Bayer-2349 (5). The work was done at the Institute of Hygiene, Marcel Wanson, Leopoldville, Belgian Congo and it represented the first organophosphorous compound used in human therapy, except for small trials of similar but more toxic drugs in glaucoma and myasthenia.

According to their results, Bayer-2349 was well tolerated by more than 2,000 people at dosages ranging 7.5 to 15 mg/kg/day. Their cure rates, as reported were: 70-90% in ankylostomiasis, 50-70% in ascariasis, 40% in schistosomiasis.

These results were based on relatively few post-treatment examinations and short follow-up periods. After the political events that led to the departure of Belgian civil servants from the Congo, it was difficult for the workers to gather the detailed data and information necessary for publication of their work.

Material and Methods

Patients were selected from the populous Schistosomiasis Out-Patient Clinic of the Puerto

Rico School of Medicine and the University Hospital, which is a large referral Hospital serving the Northeast region of Puerto Rico. Selected patients, of both sexes, met the following criteria of elegibility: 1) Individuals over the age of 18 years having moderate to heavy infections (preferably those with over 30 ova of *Schistosoma mansoni* per gram of stool in the concentrate), 2) untreated with any schistosomicidal drug for at least one year before starting therapy with Ronnel, and 3) free of systemic complications (i. e.: advanced ascites, pulmonary schistosomiasis, heart failure, etc.). In the case of females, pregnancy was a contraindication for inclusion in the study.

Selected patients were then subjected to a careful history (emphasizing endemic area of birth and residence, personal hygiene habits, incidence of river-bathing, episodes of rectal bleeding, hematemesis, jaundice, etc.), physical examination, rectal biopsy, three consecutives stool examinations performed by the formal-in-ether concentration techniques (6), electrocardiogram, and the following baseline laboratory work-up: blood counts, urinalysis. VDRL microfocculation, thymol turbidity, cephalin flocculation, total proteins and A/G ratio, serum protein electrophoresis, blood urea nitrogen, urine urobilinogen, RBC cholinesterase, and serum oxaloacetic and pyruvic transaminases.

Patients were admitted for a period of one week to the Clinical Research Center of the School of Medicine where they remained ambulatory, on a regular diet and closely supervised by the medical staff. No medications other than that of the study was given to them during their hospital stay. Cases were usually admitted in pairs.

The study was initially conducted in a double-blind fashion. Placebo tablets were manufactured to look exactly like the Ronnel 250 mgm tablets. The placebo and Ronnel tablets* were individually packaged in separate vials and assigned a code number by the manufacturer. The code was kept in a sealed envelope, thus preventing knowledge by the physician, nurse or patient of the nature of the tablets dispensed. The coded vials were then assigned at random, chronological ascending fashion to groups of selected patients, who were divided in groups of ten in order to increase dosage with each succesive group. The initial dosage was 1,250 mg daily taken at one time for three consecutive days one hour after breakfast. A working order sheet was designed and inserted into each patient's chart to avoid errors in daily procedures of the nursing staff.

A toxicity report sheet was designed where all side effects observed were recorded daily by the physician and nurses. No specific questions on side effects were asked to the patients in order to avoid bias. Instead, all toxic effects were either objectively observed by the physician and nurses or subjectively reported on a voluntary basis by the patient himself.

Daily stool examination and RBC cholinesterase following the 1st and 3rd dose of Ronnel were performed during the patient's hospitalization period. The serum bilirubin, BUN, thymol turbidity, cephalin flocculation, serum protein electrophoresis, CBC, urinalysis, electrocardiogram, serum transaminases, and urine urobilinogen were performed upon completion of the course of treatment.

RBC cholinesterase levels were determined on a Beckman pH-meter by the Michel method (7) and results expressed as change in pH per hour. At the end of the one-week period patients were discharged on multivitamins after being properly instructed in the following schedule of stool examination follow-up period: Twice a week for four weeks; then once a week for four weeks; followed by once a month for 10 months. Emphasis was placed on the importance of this phase of the study.

The results were analyzed upon completing treatment of 28 cases. As there was no difference between the treated and control groups, the double blind study was dropped. It was then decided to give increasing dosage of Ronnel to groups of ten patients each until a maximum of 2,000 mg daily dosage had been reached. The vials containing the old medication were collected by the manufacturer and new vials were packaged according to the new increasing dosage schedule.

Results

A) *Effect on S. mansoni egg counts in the stools:*

* *Kindly supplied by Pitman-Moore Company, Division of Dow Chemical-Indianapolis, Indiana.*

As evidenced by quantitative egg counts before and after treatment there was no significant change in the group of patients treated with daily doses ranging from 1.5 to 2.0 gm for three consecutive days. The 17 patients receiving 1,250 mg daily for three days showed a significant change from the values prior to treatment. The control group, which was treated simultaneously in a double-blind fashion, showed the same variation (Table 1).

B) *Toxicity and Tolerance*:

As evidenced by observed and reported clinical side effects (both subjective and objective) Ronnel proved to be a very safe, non-toxic drug at the dosages administered. It was tolerated well by most patients and in no case was discontinuation of therapy necessary because of adverse reactions produced. Those untoward effects produced by Ronnel fall in the category of slight and self-limited. These were principally related to the gastrointestinal tract (e.g.: nausea, vomiting, abdominal pain, anorexia and hypermotility) (Table 2). In the one case where bloody diarrhea was reported, the patient was found to have that complaint for several months prior to the beginning of Ronnel therapy. The size or number of tablets administered presented no problems with any patient.

No clinical signs of cholinesterase depression such as miosis, diaphoresis, salivation, twitching, convulsions or pulmonary edema were encountered. The RBC cholinesterase determinations remained within the limits of normal, even after treatment with the relatively high dosage of 2 grams per day for three consecutive days.

TABLE I: EGG COUNTS BEFORE AND AFTER TREATMENT

Treatment Group		No. of Cases	Eggs (number/g of stool) Before Treatment	Eggs (number/g of stool) After Treatment	Test of Significance
	Placebo	10	103 + 28.8 (27)*	46 + 7.0 (109)	Significant
I	1,250 mg	17	73 + 13.1 (41)	38 + 3.3 (207)	significant
II	1,500 mg	10	46 + 10.2 (29)	43 + 6.3 (104)	Not significant
III	1,750 mg	10	56 + 10.4 (18)	50 +16.7 (122)	Not significant
IV	2,000 mg	10	33 + 3.5 (30)	26 + 3.6 (103)	Not significant

* In parenthesis is number of stool examinations.

TABLE II: SIDE REACTIONS

Symptom	Ronnel (47 cases)	Placebo (10 cases)
Epigastrict or abdominal pain	8	0
Anorexia	4	0
Headache	4	1
Nausea	4	0
Vomitting	3	0
Dizzyness	3	0
Diarrhea	2	0
Fever	2	0
Weakness	2	0
Hyperperistalsis	1	0
Oppression of chest	1	0
Epistaxis	1	0
Periorbital edema	1	0
Hyperpnea and rash	1	0
Supra-Pubic pain	0	1

Discussion

The clinical evaluation of a schistosomicidal drug presents problems as there is no accurate way to calculate the worm load in the human being. One must depend on the appearance of fresh eggs in the stools or the rectal mucosa to determine if the worm is still present. The accuracy of the quantitative stool counts is variable, becoming less efficient with decreasing egg counts. The activity of oviposition of the female parasite seems also to be variable. To compensate for these variables one must depend on numerous egg counts and the use of control cases.

The results on the cases treated with 1250 mg showed that there was a significant change in the egg counts before and after treatment. If the control group had not been present, this effect could have been attributed to the drug. It seems to us that for the evaluation of drugs in schistosomiasis a control group should always be included and cases followed from 6 to 12 months, as transitory depression of oviposition may occur.

Summary

Ronnel, an oral organo-phosphate drug was used in a clinical trial involving 57 patients with *Schistosomiasis mansoni*. It was given in increasing dosages ranging from 1,250 to 2,000 mgm daily for three consecutive days. Its efficacy in suppressing oviposition was minimal or absent, although it proved to be remarkably nontoxic, both from the clinical observations and as evidenced by the absence of significant depression of red blood cells cholinesterase.

Resumen

Ronnel, un fármaco de fósforo oral, se usó en un ensayo clínico que incluyó cincuenta y siete pacientes con esquistosomiasis mansoni. Fue administrado en dosificaciones que variaron de 1,250 a 2,000 mgm diario por tres días consecutivos. Su eficacia en suprimir oviposición fue mínima o ausente, aunque resultó ser extremadamente inocua, evidenciado por las observaciones clínicas y por la ausencia de disminución significativa en la colinesterasa de los hematíes.

Acknowledgement

The contribution of Miss Gladys Sánchez, M. T., Miss Milagros Maldonado, R. N., and Miss Raquel Torres, M. S. is gratefully acknowledged.

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CARDIAC CATHETERIZATION
A REVIEW

J. E. Lugo, M.D.

A catheter is a tube made of polyethylene, teflon, nylon or any other suitable material which can be inserted through a blood vessel (vein or artery) into a large blood vessel and into the heart. It is usually radiopaque and its course is visualized on a fluoroscope, image amplifier or TV screen. Several kinds of catheters are available (for different uses): with open or closed ends, bends; of thickness and length of varying degree. The patient, if a child, requires premedication and general anesthesia; if an adult, only premedication and local anesthesia.

Discomfort may be present at the catheter entrance site because of blood vessel spasm, but this is generally tolerable. The procedure may last from 2-4 hours depending on the nature of the disease and the study attempted. During the procedure the electrocardiogram and the systemic arterial blood pressure (via an indwelling needle), are observed in an oscilloscope to monitor the patient's cardiovascular status at all times (Fig. 1). There is a small risk of infection, intravascular clotting, damage to the heart by the catheter or production of cardiac arrhythmias. Therefore, a permit is required as for a surgical procedure and a catheterization is not undertaken unless the need for it is clearly demonstrated.



Fig. 1: The Cardiac Catheterization Laboratory (University Hospital). Notice the image intensifier, attached to the conventional fluoroscope in the center of the picture. Also notice the oscilloscope where both instantaneous electrocardiogram and pressure tracings may be observed. One or two television sets may be attached to the system for group visualization of the catheter.

Usefulness

Catheterization is useful to determine the anatomic and physiologic changes produced by both congenital and acquired heart dis-

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ease. Also, it helps determine the physiologic changes of exercise, drugs, heart surgery, oxygen inhalation, or disease of the heart itself or other organs. It can be used to study the blood vessels and outline arterial defects such as a coarctation of the aorta or stenosis of a renal vessel and to show acquired disease such as pulmonary embolism. The data obtained by cardiac catheterization also can be used to determine valve areas, defect sizes, magnitude of shunts, ventricular work, resistances, and cardiac outputs.

Because of its many uses and applications, the procedure is not standardized for any case and sometimes has to be modified during its course, to clarify the findings as they are obtained. Several persons are necessary to perform a cardiac catheterization; each one being responsible for a facet or activity of the procedure.

Definitions

The following are common terms in a catheterization:

Right sided catheterization: The catheter is introduced via a vein into the right side of the heart, up to the pulmonary artery.

Left sided catheterization: The catheter is introduced into the left side of the heart (left ventricle, left atrium, aorta).

Transeptal catheterization: Through a right sided catheterization a catheter is passed from the right to the left atri um by use of a needle puncture of the interatrial septum.

Retrograde catheterization: Through an artery the catheter is introduced back into the heart.

Percutaneous catheterization: To pass a catheter into a blood vessel without requiring incision of the skin.

Measurements at Cardiac Catheterization

Generally, five studies are performed:

1. Pressures (Fig. 2, 3).
2. Oxygen content (Fig. 3).
3. Cardiac output.
4. Indicator dilution curves.
5. Angiocardiography.

A. *Pressures* — (Fig. 2) The measurement of systolic, diastolic and mean pressures will determine the presence of stricture or stenosis of a valve or vessel. (The pressure below an obstruction is higher: beyond, lower). Also, a study of the pressure *tracing* may help in ascertaining the presence of cardiac failure, valvular insufficiency, pericarditis, or the location of the catheter tip as each chamber produces a "typical" curve and the contour is affected by disease.

B. *Oximetry* — Oximetry will show peripheral desaturation as is seen in cyanotic heart disease; or a left to right shunt if it demonstrates an abnormal oxygen decrease in saturation in the right side of the heart.

C. *Cardiac output* — A cardiac output is the determination of the flow of blood through the aorta in liters per minute.

D. *Dilution curves* — The dilution curves will demonstrate *shunts* in either direction. They may be altered by valvular insufficiency or cardiac failure, presenting characteristic curves. A series of curves are usually performed with injection of dye in different chambers and collecting this dye at the arterial side of the circulation as it flows through a densitometer.

E. *Angiocardiography* — Angiocardio-

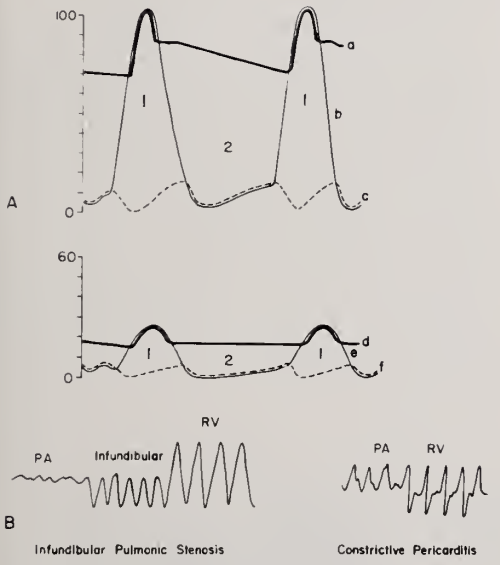


Fig. 2: Pressure Tracings in the Normal and Abnormal Heart. A— Schematic drawing of six instantaneous *normal human heart pressure* tracings: a— aorta; b— left ventricle; c— left atrium; d— pulmonary artery; e— right ventricle; f— right atrium. 1— systole; 2— diastole. Notice *similarity* of contour in arterial, ventricular, and atrial tracings of the two sides of the heart, but difference in amplitude.

B— Diagrammatic reproduction of "pressure pullback" tracings in two *diseased hearts* following withdrawal of the catheter from pulmonary artery to right ventricle.

Left — infundibular pulmonic stenosis as seen in Tetralogy of Fallot. Notice similarity in contour of infundibular area tracing and right ventricular (RV) tracing (meaning that there is an intermediate (infundibular) chamber between the ventricle and pulmonary artery (PA).

Right — Pulmonary artery (PA) and right ventricular (RV) tracing as seen in an actual case of constrictive pericarditis. The "early dip in diastole" in the ventricular tracing is characteristic, though not pathognomonic of the disease.

grams will show the *anatomic detail* of the blood vessel or heart chamber studied. Recordings made in cine film, video tape or roll films either in one or two planes can be obtained.

Description of the Procedure and Normal Values

1. *Pressures* — (Fig. 3). To determine pressures a pressure transducer is used to receive the impulses, which are then observed on an oscilloscope and recorded permanently. Both systolic, diastolic, and mean

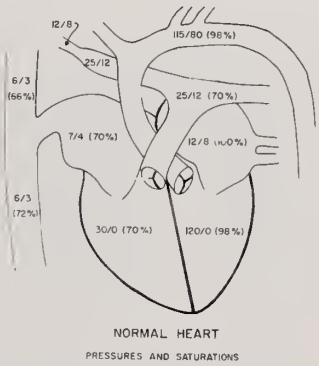


Fig. 3: Normal Heart — Pressures and Saturations. The slightly different pressures given in the nest belong to another normal patient. Saturations are in parenthesis.

pressure readings are desirable. Normal values depend on the chamber or vessel studied. Commonly used abbreviations for the different chambers follow:

SVC — Superior vena cava
IVC — Inferior vena cava
RA — Right atrium
RV — Right ventricle
PA — Pulmonary artery
LA — Left atrium
LV — Left ventricle

The normal or "average" values are (Means are in parenthesis):

Aorta — 120/80 (92) mm Hg
LV — 125/0 mm Hg
RV — 25/0 mm Hg
PA — 20/10 (15) mm Hg
LA — 12/6 (8) mm Hg
RA — 7/3 (5) mm Hg
SVC— 7/3 (5) mm Hg
IVC— 7/3 (5) mm Hg

2. *Oximetry* — (Fig. 3). The oxygen content of the blood in any chamber studied is determined instantly (by an oximeter), or later (by an spectrophotometer or Van-Slyke analysis).

The normal values are:
Right side (SVC, IVC, RA, RV, PA) .....
65 — 75% saturation.
Lift side (LA, LV, aorta) .....
95% or higher.
An increase in saturation at any level, if it keeps constant ahead, suggests a left to right shunt at that level; provided it is a high enough rise (0.5 - - 1.5 vol. %)

3. *Cardiac output* — This is determined either by the Fick principle or by computer analysis of dye curves or other methods. The following formula is used:

$$\text{Cardiac Output (Liters/Min)} = \frac{O_2 \text{ Used (Ml/Min)}}{\text{A-V Oxygen Dif. (Vol\%) X10}} =$$

$$\frac{250}{(15.0 - 10.0) \text{ X } 10} = \frac{5.000}{\text{L/Min}}$$

Oxygen used — 250 Ml/Min. - Analysis of expired air
Systemic Arterial Saturation - 15.0 Vol%
- Saturation of blood
Pulmonary Arterial Saturation - 10.0 Vol.%
- Saturation of blood

Normal — Males = 4/L min.
Females = 3.5/L min.

The cardiac output varies with the patients size, and thus a *cardiac index* is preferred which gives cardiac output per square meter of body surface area.

$$\text{Cardiac Index} = \frac{\text{Cardiac output}}{\text{Body surface area}} = \text{L/min/M}^2$$

4. *Dilution curves* — (Fig. 4) Similar in principle to a circulation time, they are performed as follows:

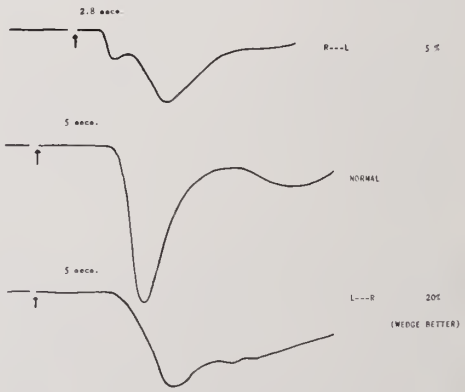


Fig. 4: Normal Indicator (Dye) Curves Compared to Curves With Right to Left and Left to Right Shunts. Right to left shunts as small as 5% and left to right shunts as small as 20% of the systemic flow, can usually be detected by dye dilution curves. For explanations of the curves, refer to text.

a. A substance is introduced into a vessel or chamber of the heart to determine its circulation pathway.

b. The changing concentration of the substance in time is determined at a peripheral artery in a continuous graph, till it dissappears from the circulation.

c. Series of curves are performed (from the different chambers) to determine *comparative* circulation pathways.

Several abnormal characteristics may be evident in the comparison of curves from different chambers:

(1) *Short appearance time* — This generally means that the dye went from right to left without going to the lungs*. Therefore, a short appearance time diagnoses a right to left shunt at the particular chamber studied, if the appearance time in the next chamber of the right heart is longer.

(2) *Long appearance time* — This usually means slow circulation or cardiac failure.

(3) *Low peaks* — They suggest great dilution, slow transit or low output.

(4) *Shunts* — The characteristics follow: *L to R shunt*: (refer to Fig. 4) (Re-circulation is disturbed by a vicious circle through the lungs) The L to R shunt will not appear in the curve performed from the chamber *beyond* the shunt).

R To L shunt (refer to Fig. 4) (short appearance time with an *early* low peak which shows amount of dye that went across, through abnormal R to L pathway. The R to L shunt will not appear in the curve recorded *beyond* the shunt.

5. Angiocardiography — In angiocardiogram (Fig. 5) a radiopaque dye in high concentration is injected peripherally or

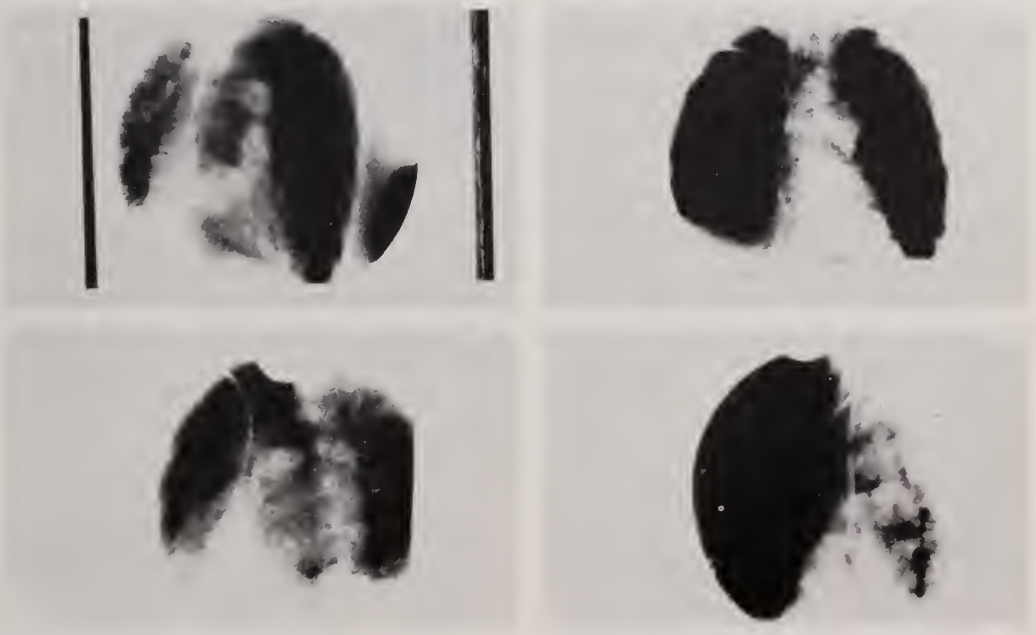


Fig. 5: Palateral Angiocardiogram in cases of valvular pulmonic stenosis (left) and tetralogy of fallot (right). Notice on the left the stenotic pulmonic valve. Notice on the right the infundibular area and early opacification of the aorta (PA view); and the ventricular septal defect and relative position of the great vessels (lateral view).

* Except when there is a pulmonary A-V fistula, when the shunt therefore, *occurs at the level of the lungs.*

selectively in a chamber, usually under pressure. The passage of the dye is recorded in cine or X-ray film for further study. The study will show the anatomic details of location of the chambers, blood vessels, valvular defects, etc.

Sample Catheterization

The following is an example of a catheterization report in a case of an atrial septal defect of the typical ostium secundum type performed at our Laboratory. Pressure measurements, oximetry, dye dilution curves and angiograms were performed.

A. Results:

1. *Pressures and Saturations*

Position	Pressure (mmHg)	Saturation (%)
SVC	7/3 (5)	68%
IVC	7/3 (5)	70%
HRA	7/3 (5)	69%
MRA	7/3 (5)	81%
LRA	7/3 (5)	79%
RV	30/0	80%
PA	25/12 (16)	80%
LA	9/5 (7)	96%
FA	120/80 (92	95%

2. *Dye dilution curves, calculations, and Angiocardiograms*:

a. Dilution curves — performed up to the left atrium. All showed a L to R shunt.

b. Calculations — Pulmonary flow — 14 L/min. Systemic flow — 4 L/min.
L to R shunt — 10 L/min.

c. Angiocardiograms - From LA shows atrial septal defect with L to R shunt into RA (Fig. 6).

B. Interpretation:

Notice the following considerations:

1. The left atrium was catheterized (from the right atrium through an atrial septal defect).



Fig. 6: Left Atrial Angiocardiogram in a Patient with an atrial septal defect lateral position). Notice the flow of blood from the left to the right atrium: upper right corner — left atrium; upper left corner — right atrium; lower right corner — left ventricle.

2. The small difference in pressure from right ventricle to pulmonary artery does not represent stenosis of the pulmonic valve and is due to increased flow through the valve.
3. The increase in saturation at the mid right atrium is carried forward to the pulmonary artery virtually unchanged, localizing a L to R shunt at the atrial level.
4. The "pulmonary flow" is increased by the shunt (creating a vicious cycle of 10 extra liters per minute).
5. The left side of the heart has a normal saturation.

CALCULATIONS OF PULMONARY AND SYSTEMIC FLOWS AND OF THE LEFT TO RIGHT SHUNT IN A PATIENT WITH AN ATRIAL SEPTAL

$$\text{A. Systemic flow} = \frac{\text{Oxygen Consumption (ml/min)}}{\text{Systemic Saturation- mixed Venous Blood x 10 Saturation (vol/\%)}} = \frac{160}{\text{16-12 (4) x 10}} = 4 \text{ liters/minute}$$

$$\text{B. Pulmonary flow} = \frac{\text{Oxygen Consumption (ml/min)}}{\text{Pulmonary artery saturation (vol/\%) x10}} = \frac{160}{\text{16-14.8 (1.1) x10}} = 4 \text{ liters/minute}$$

C. Left to right shunt = Pulmonary - Systemic Flow (L/min) = 14 - 4 = 10 L/min.

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GRAND ROUNDS
UNIVERSITY HOSPITAL

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Clinical Abstract

A 24 year old white male, known case of systemic lupus erythematosus, was admitted for the third time to the University Hospital, complaining of chest pain and shortness of breath.

The history of the present illness dated back to 1960, when he developed swelling, redness and increased heat of both elbows. He was seen by a private physician who treated him with salicylates and penicillin injections for a recent gonococcal urethritis. He improved but continued with the same symptomatology on and off for the next two years. On February 1962, he was seen at the Guaynabo Research Clinic. At that time he gave history of pain and swelling of both elbows, pain of the metacarpophalangeal joints, and occasional shoulder and knee pain. He had been treated with salicylates, Aralen, and cortisone on and off with some improvement. At that time he was found to have bilateral effusion of the elbows and tenderness on both wrists and was diagnosed as definite rheumatoid arthritis. He was treated with salicylates which gave some improvement but symptoms continued to reappear periodically. Shortly after he was convicted for addiction and was sent to Lexington, Kentucky. There he again developed swelling, increase heat and redness of the knees and elbows. He was re-started on salicylate treatment with some improvement. A year later, he was transfered to Synanon Convalescence Home in California. While there he developed weakness, swelling and increased heat of the knees, ankle and elbows, fever, loss of scalp hair, a butterfly malar rash, an erythematous rash of the upper trunk and bleeding from the gums and lips. He was hospitalized at Los Angeles Hospital where he was told to have lupus erythematous and was started on prednisone therapy which brought about some improvement.

A year and a half ago he returned to Puerto Rico. A private physician treated him with prednisone, but discontinued it because he developed moon-facies. During this time a positive serology was found and he was treated with penicillin. He started working in a construction industry where he was constantly exposed to the sungliht. He developed a skin rash, arthralgias, fever, loss of scalp hair and generalized weakness. He became depressed, quit working, discontinued all medications and resumed his addiction to narcotics. Six months ago he was

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sent to the state prison. There he developed generalized malaise, fever, arthralgias ulceration of the lips, severe frontal headaches and blurring of vision. A month later he started noticing progressive swelling of the legs and abdomen. Later on he developed high fever, chills, burning in urination, frequency and oliguria. He was treated with some red pills for the urinary infection with no avail.

On March 2, 1966 he was referred to the University Hospital where he was admitted with the diagnostic impression of lupoid nephritis with superimposed acute pyelonephritis.

Upon admission he was found to be febrile, chronically ill and presented edema of the face, arms, abdomen and legs. He had a large ulcer in the buccal mucosa and the liver was felt three centimeters below the right costal margin. Pertinent laboratory findings revealed hematuria, albuminuria, pyuria azotemia and hypoprotenemia. He was started on prednisone 60 mg. daily, erythromycin, sulfisoxazole and a low salt diet. Two days after admission the patient developed signs of congestive heart failure and was digitalized. Later on, because of persistent albuminuria, no weight loss, and low serum proteins he was given salt-free human albumin infusions and prednisone was increased to 80 mgs per day. At that time isoniazid was added to the therapy.

For the next two weeks he did not improve much. He did not lose weight, significantly, continued with marked albuminuria, hypoprotenemia and azotemia. He was kept on prednisone 80 mg daily and chloroquine phosphate 500 mgs. daily; polythiazide 4 mgs. was added to the therapy. He was given several salt free human albumin infusions and kept on restricted fluid intake. (Table II). Hemorrahgic purpuric lesions appeared in the genitalia and inner thighs. At that time erythromycin was changed to methicillin and two blood transfusions were given. As it was the feeling of the staff that the patient was not improving prednisolone 25 mg intramuscularly twice a day was added to the above therapy. By mistake the prednisone was not given for almost a week and he only received the prednisolone added. He deteriorated rapidly, developed a left pleural effusion and became frankly psychotic with hallucinations and bizarre behavior. At this time the possibility of steroid induced psychosis was considered but when it was found that he was not receiving the prednisone it was decided to increase the prednisone to 100 mg daily because of the possibility of cerebral vasculitis.

A week later he was definitely improved. He was mentally clear, had lost 19 pounds of weight and the pleural effusion had disappeared. The BUN dropped to 29 mgs.% and the albuminuria, had decreased in amount. At this time the digitalis and the isoniazid were discontinued. He continued improving clinically although no further weight loss was observed and the serum proteins dropped again. Human albumin salt-free infusions were given on March 18 and 26 (Table II). He improved and was discharged on May 29, 1966.

In his clinic visits to the Rheumatology Clinic, he showed increasing edema and weight gain. Prednisone was gradually reduced, and the diuretic was changed. On June the 1st., he complained of a dull chest pain and moderate shortness of breath. A chest film revealed diffuse interstitial pneu-

monitis of the left lung and tuberculosis was considered as a diagnostic possibility by the radiologist. He was seen one week later and was found to be much improved. Repeated chest films were negative.

On July 20, 1966 he was admitted for the second time as an elective admission to receive salt free albumin infusions for the persistent hypoalbuminemia. (Fig. 1). At that time he gave history of progressive



Fig. 1: Serum electrophoresis. This serum electrophoresis was done on the first admission to the University Hospital. It shows an extremely low albumin level with an increase in all the globulin fractions. (T.P. 3.9 g/100 ml. Albumin, 18.2%; α_1, 7.3%; α_2, 17.1%; β 23.2%; γ, 34.2%).

anorexia, insomnia, lassitude and generalized weakness. He also claimed an episode of sudden unconsciousness that lasted for 20 minutes with no further recurrence. He was hospitalized for eight days and received five salt-free human albumin infusions. He ran an afebrile course and lost nine pounds of weight. The 24 hrs. urine for protein dropped from 9.3 g to 1.3 g per 24 hours in five days (Table I). He was discharged on July 28, 1966 on prednisone 50 mgs. daily, chloroquine phosphate, trichlormethiazide and isoniazid.

TABLE I: URINE PROTEINS RECEIVING ALBUMIN INFUSIONS

Date	Urine protein (g/day)	Albumin Infusion (g)	Weight (lb.)
July 19	9.3	12.5	144
July 22	6.1	12.5	—
July 23	5.1	12.5	—
July 25	2.9	12.5	138
July 26	1.3	12.5	135

On August 9, 1966 he was admitted for the third time because of low grade fever, dry hacking cough, shortness of breath and substernal pain of three days duration. On physical examination he was found to have a blood presure of 130/70, pulse 120/minute, regular and temperature 36.8°C. His chest was clear and the heart was found to be enlarged. The liver was felt 3 finger breadths below the right costal margin and he had grade II pitting pretibial edema. The pertinent laboratory findings in this admission revealed: hemoglobulin of 7.2% WBC, 19,850/mm^3, segs. 65% stabs. 18%, juvenile 4%, lymphs 5%. The hematocrit was 24%, the urinalysis showed 2+ albumin, WBC 2–4/HPF, RBC 5–10/HPF, 6 to 8 granular casts. The serum sodium was 134 mEq/L, the serum potassium 4.3 mEq/L, the chlorides 107 mEq/L and the CO_2 combining power 23 mEq/L. The BUN was 54mg %, the serum proteins was 5.25 gm %, albumin 3.1 gm %, globulin 2.15 gms. %. Six blood cultures taken were negative. The uric acid was 8.7 mgs. % and the latex fixation test positive to 1:640 dilution. LE. cell tests were repeatedly positive (Fig. 2) and the fluorescent antinuclear antibody test was positive (Figs. 3 and 4). The electrocardiogram on admission re-

TABLE II: LABORATORY DATA AND THERAPY

Date	Weight (lb)	Serum Proteins (g/100 ml)		Urine Protein (g/day)	BUN (mg/100 ml)	Electrolytes (mEq/L)				Treatment
		Albumin	Globulin			Na	K	Cl	CO_2	
3-3-66	143	1.8	2.1	-	89	130	5.2	119	10.2	Prednisone
3-7-66	-	-	-	2.6	101	-	-	-	-	Albumin infusions x3
3-18-66	143	2.8	1.8	10.1	92	138	6.0	-	-	Polythiazide Albumin infusions Prednisone 80 mg
3-26-66	125	3.4	1.1	3.7	83	140	4.7	108	15	Prednisone 80 mg Chloroquine phosphate Polythiazide Blood transfusion Albumin infusion
4-4-66	122	1.7	1.8	4.1	34	133	4.5	115	16.8	Prednisone 100 mg Polythiazide Chloroquine phosphate
4-15-66	132	1.9	1.3	6.8	44	135	4.3	118	21.3	Prednisone 90 mg Polythiazide Chloroquine phosphate
7-13-66	144	2.3	2.0	-	40	125	4.8	117	17	Prednisone 60 mg Chloroquine phosphate Trichlormethiazide
7-26-66	135	2.3	1.3	-	-	140	3.3	105	21	Prednisone 45 mg Trichlormethiazide Chloroquine phosphate
8-10-66	-	3.1	2.2	-	-	131	4.3	107	23	Prednisone 60 mg Trichlormethiazide Chloroquine phosphate

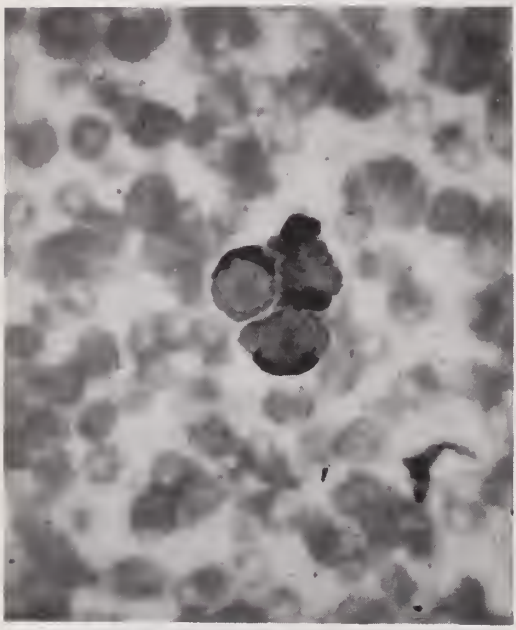


Fig. 2: L.E. cell preparation.

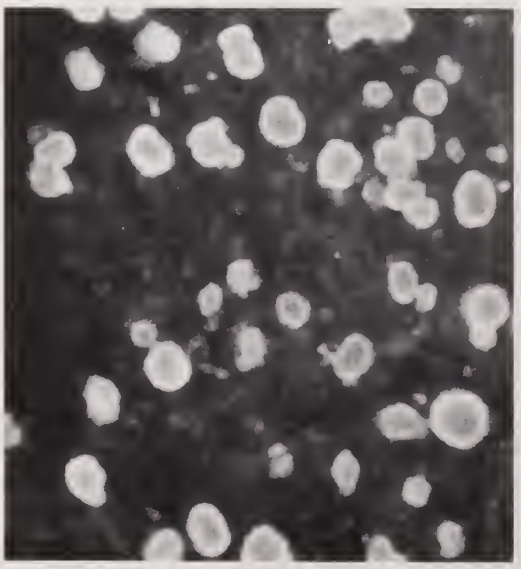


Fig. 3: Antinuclear antibody test-peripheral pattern. The staining is mostly around the periphery of the nucleus.

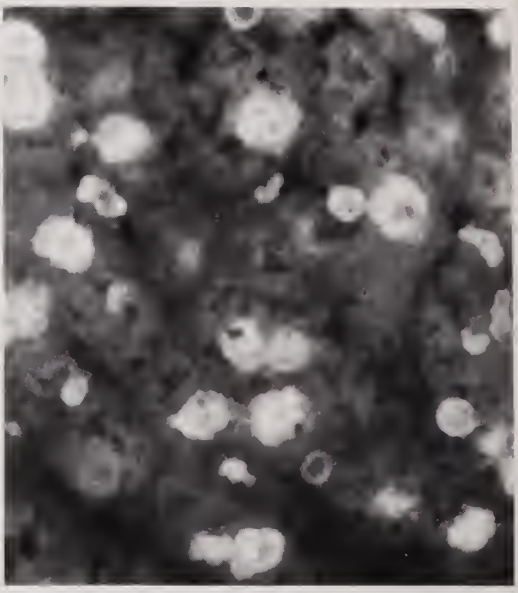


Fig. 4: Antinuclear antibody test-cluster of spheres pattern. This test was done 3 months after the first one (Fig. 3). The pattern of fluorescence varies with the activity of the patient. The peripheral is mostly seen in really active patients.

vealed a rate of 148/minute, regular, non specific ST-T wave changes and slight prolongation of the PR interval. Chest film revealed enlargement of the heart and interstitial pneumonitis at the left apex and the right lung base. The patient was placed on cephalothin 1g every 4 hours and chloroquine phosphate 250 mg. twice a day. His condition deteriorated and it was decided to digitalize him. In spite of this he has continued with the rapid pulse.

Discussion

Dr. Esther N. Gonzalez: This case was selected for presentation because he shows most of the manifestations that are seen in

systemic lupus erythematosus. This is a twenty-four years old male whose present illness dates back to age seventeen. At that time, because of history of exposure, he was thought to have a gonococcal arthritis. However, he was treated with penicillin, and did not improve. The therapy was switched to salicylates, and he improved slightly of his arthritis. Two years later, we saw him at the Guaynabo Research Clinic. At that time he had arthritis of his elbows, shoulders and knees and was diagnosed as a definite case of rheumatoid arthritis. He was treated with salicylate but we only saw him twice and he disappeared. He became a drug-addict and left for the United States. In the United States he continued with his joint symptomatology and he was again treated with salicylates.

One of the most common and characteristic manifestation of systemic lupus erythematosus is joint involvement. In most series, arthralgias are present in over 1/3 of the cases while objective joint changes are seen in half of the cases. The articular manifestations may be fleeting, may undergo recurrences or may run a course identical to that of rheumatoid arthritis. It is because of this that some observers have claimed that rheumatoid arthritis and lupus are therefore one disease with different clinical manifestations. However, I must say, that it is generally accepted that both are different conditions clinically and inmunologically. Some patients may have the clinical picture of rheumatoid arthritis for years before the diagnosis of lupus is made. It is not until the picture of a multisystem disease develops that you can make the diagnosis of lupus. Unless they have multiple systems involvement, and as long as the manifestations are limited to the joints you have to call them rheumatoid arthritis. The joints which are more affected are the wrists, the proximal interphalangeal joints, the elbows, the shoulders and the knees.

This man was a year later transferred to California and there he developed weakness, edema, fever, loss of scalp hair, a butterfly malar rash and an erythematous rash of the upper trunk. The patient now manifested the first clinical indication that he did not have plain rheumatoid arthritis but that he had systemic lupus erythematosus. Skin manifestations are not seen in the adult type of rheumatoid arthritis. Only in patients with juvenile rheumatoid arthritis are skin manifestations occasionally seen. In the latter the skin manifestations are mainly a maculopapular rash that appears on the trunk and upper extremities when the patient is very febrile. Cutaneous manifestations in patients with lupus occur at one time or another during the course of the disease in 90% of the patients. The most frequent cutaneous lesions are the erythema of the malar area and bridge of the nose. Some patients in addition, develop maculopapular eruption with fine scaling in the same region, commonly named the butterfly rash. The second most frequent skin manifestations in our patients is alopecia. We have seen alopecia in about seventy five percent of our patients with lupus. The alopecia may be patchy, may be diffuse, may be mild or may be severe. Alopecia usually occurs when they are very ill and tends to disappear as the disease goes into remission. Usually the hair grows in again, but occasionally there is one or two patients who fail to have their hair grow back. Photosensitivity is very frequent in our patients, pro-

bably because in our tropical area the sunlight is so bright the year round. Photosensitivity is seen in about a third of all patients with lupus. Our patient gave a history of photosensivity. Discoid lupus may be the presenting manifestations in patients with systemic lupus in about 10% of the patients. However, we know that about 20% of all patients with systemic lupus do have chronic discoid lesions of the skin. Raynaud's phenomena are seen in 20% of the cases. At times the vasospastic changes precede the overt clinical manifestations of the disease for many years. Petechia, purpura, and ecchymosis of the skin are seen in about 20% of the cases. These ecchymotic and purpuric lesions of the skin may be due, mainly, to three factors; 1) secondary to steroid therapy which is the most frequent cause; 2) angiitis, and 3) thrombocytopenic purpura which occurs in about 8% of all patients with lupus. Mucous membrane lesions, like shallow ulcerations and palatal erythema also occur during periods of activity. Less frequent manifestations of cutaneous involvement are: pigmentation, skin ulcers, subcutaneous nodules and gangrene. I must say that we have seen all of these cutaneous manifestations in our patients with lupus. Treatment with prednisone was instituted in California and he improved considerably his clinical picture. The patient returned to Puerto Rico and went back to drug addiction. He was sent to the state prison. While in prison he developed an acute exacerbation of his symptomatology accompanied this time with severe headache and blurring of vision. He was referred to the University District Hospital. On physical examination he was febrile, looked chronically ill and had edema of the face, arms abdomen and legs. He had a large buccal mucosal ulcer and the liver was felt three centimeters below the right costal margin. Laboratory work-up revealed hematuria, albuminuria, pyuria, azotemia and hypoprotenemia.

The above symptomatology and laboratory findings, pointed toward the development of lupus nephritis. Kidney involvement occurs in 60-70% of all patients with lupus erythematosus. In our patients we have a 60% incidence. It may be manifested by only mild proteinuria or by more severe signs like hematuria, severe proteinuria, and azotemia. The course of lupus nephritis is extremely variable since patients may have proteinuria for years before other features such as the nephrotic syndrome, hypertension or uremia appears. On the other hand, some individuals have a fulminant course and die of renal insufficiency in few weeks after the clinical onset of the manifestations.

Pathologically five lesions are responsible for the clinical picture that patients with renal involvement develop. The first is focal glomerulitis. Patients who have this pathologic lesion clasically show hematuria which may be more or less severe. This condition may disappear with therapy, and patients may remain asymptomatic for many months if they are adequately controlled. The second important lesion that is seen in the kidney of patients with renal disease is a lesion indistinguishable from subacute glomerulonephritis. Patients who develop this pathologic lesion in the kidney have a very fulminant course. They have what we call lupus glomerulonephritis. No matter what we do for these patients, the course is very rapid and they die soon after the condi-

tion is diagnosed. The life of these patients can be prolonged more or less with adequate therapy, but they die before two years after the diagnosis of lupus glomerulonephritis is made.

The third important lesion is membranous glomerulitis. Membranous glomerulitis is responsible for the clinical picture of nephrotic syndrome in lupus. It is principally characterized by thickening of the basement membrane. Membranous glomerulitis produces nephrotic syndrome in lupus which is a little bit different from the nephrotic syndrome that one sees secondary to glomerulonephritis, poisons, syphilis and so forth. For one thing these patients may have the full syndrome with hypoalbuminemia, marked albuminuria and yet very little edema. Secondly patients with lupus who have the nephrotic syndrome may have high, normal or low cholesterol. It is a known fact that patient with the usual type of nephrosis have hypercholesterolemia. It has been the impression of the people who have worked with this type of condition that the patient with lupus nephrosis who have a high cholesterol have a poorer prognosis than the one who has a normal or low cholesterol. The fourth renal pathologic lesion is focal hypercellularity. It is a milder lesion that is seen in patients who have mild albuminuria and this focal hypercellularity may disappear with adequate therapy. The fifth lesions is the wire loop lesion that has long been related to systemic lupus erythematosus. The wire loop lesion per se is not responsible for any specific clinical picture of renal lupus. It is found in any of the above conditions that I have mentioned. It might be found in patients who clinically do not present renal involvement, but that on autopsy are found to have wire loop lesion in spite of the fact that during life they didn't show evidence of renal disease.

This patient was treated with steroids but did not seem to improve much with the dose given. Thus, we decided to increase prednisone to 80 mg. daily, in an effort to improve his renal condition. He also was given salt-free human albumin infusions. He developed hemorrhagic purpuric lesions of the genitalia and inner thighs and it was our feeling that his conditon was not under control and we decided to give prednisone 25 mg. intramuscularly twice a day in addition to his present therapy. One week later instead of improving the patient got worse. He deteriorated rapidly, developed a left pleural effusion and became frankly psychotic. When he became frankly psychotic we considered the possibility of steroid induced psychosis. But we found out that this deterioration was due to dis continuation of the oral Meticorten he was supposed to get for the last week. So, immediately we re-instituted therapy, and he improved. This brings us to two additional clinical manifestations in these patients with systemic lupus, which are, pulmonary manifestations and central nervous system involvement. Central nervous system manifestations in lupus occurs in around 50% of all patients at one time or another during the course of the disease. They may be neurologic or psychiatric manifestations. The neurologic group are: seizures, which are the most common manifestations, cranial nerve abnormalities, hemiparesis, paraplegia, peripheral neuropathy, paresthesias, autonomic abnormalities and mental changes. Psychiatric manifestations in lupus have been described by the psychiatrists in four categories. The first

one is organic brain reaction. The organic brain reaction may be pure or may be mixed. The pure organic brain reaction is characterized by loss of memory, confusion, difficulty in orientation, vague delusional and behavioral disturbances. The mixed organic brain reaction is characterized by all the above mentioned symptomatology plus, hallucinations and delusions. Clinically it is very difficult to differentiate the mixed organic brain reaction from an acute episode of schizophrenia. I believe our patient mental status belongs to this category, mixed organic brain reaction. The second important psychiatric manifestation is steroid induced psychosis. It is very difficult at times to distinguish between steroid induced psychosis and psychiatric manifestations secondary to systemic lupus. It is very important to determine the onset of the manifestations in relation to therapy and to dosification. In our patient after careful investigation of what was going on, we found out that it was due to a decrease in the steroid therapy. At time it is a little bit more difficult, so that careful questioning of the family by the physician who is taking care of the patient must be done to determine whether he is suffering or not from a steroid induced psychosis.

A week later this patient was completely improved, he was mentally clear, he had lost 19 pounds of weight, the pleural effusion had disappeared, and the BUN dropped to 29 mg./100ml. At this time digitalis and isoniazid were discontinued. He was seen in our arthritis clinic and his condition was more or less the same. He did show some increase of swelling and some weight gain. On May 30, he complained of dull chest pain and moderate shortness of breath. The chest film revealed diffuse interstitial pneumonitis of the left lung and tuberculosis was considered as a diagnostic possibility by the radiologist. So, he was restarted or isoniazid and prednisone was increased to 50mg. daily. At this time some observers felt that he had tuberculosis. In any patient, who is as ill as he is and is getting as much steroid as he is and with infiltration of the nature that he shows, one must consider either bacterial infection or tuberculosis. However, knowing that pneumonitic infiltrations occur in patients with lupus, we decided to start the isoniazid and to re-evaluate him in one week. One week later the chest film was completely clear.

Involvement of the pleura and lungs in systemic lupus, have long been recognized. In most series pleuritis or a pleural effusion is present in about one half of the cases and pulmonary infiltrates in about one third. Pleurisy may be the initial manifestation of systemic lupus in some patients and in others it commonly occurs relatively early in the course of the disease. The appearence of pleurisy is often followed by the accumulation of a pleural effusion with the characteristics of a transudate. Patients with pleuritis alone, at times have negative X-rays. Fleeting Pneumonitis are common in lupus and I would say that about one third of our patients develop fleeting pneumonitis which most of the time are recognized as infectious processes. I will not go into the discussion of the pneumonic infiltration of the lungs because Dr. Díaz Bonnet is going to describe the X-rays findings in this patient. He was re-admitted to the hospital on July 20 to treat him with salt-free human albumin infusions in an effort to increase his diuresis and to reduce his albuminuria. He

lost 9 pounds of edema fluid and he was discharged improved.

On August 9 he was admitted for the third time because of low grade fever, dry hacking cough, shortness of breath and substernal pain of three days duration.

He was found to have a normal blood pressure with an increased pulse rate. He was mildly orthopneic and although his chest was clear, the heart was found to be enlarged. The liver was felt three finger-breaths below the right costal margin and he had grade two pitting edema of the legs.

The electrocardiogram on admission revealed a rate of 148 per minute, regular, with non-specific ST-T wave changes and slight prolongation of the PR interval. The chest films confirmed the findings of heart enlargement and an interstitial pneumonitis was seen at the left apex and the right lung base. At this time with the history, the physical findings and the electrocardiographic findings we made the diagnosis of a myocarditis and he was admitted.

About 50% of all patients with systemic lupus develop, at sometime during their disease, detectable evidence of heart involvement. Pericarditis with effusion, myocarditis, and endocarditis are seen in this order of frequency. Involvement of the valves, the valves rings, the endocardium, the pericardium, and the myocardium in lupus is seen when the pathologic examination of the heart is done. The clinical diagnosis is made on the basis of the findings of enlargement of the heart, murmurs, congestive heart failure, rapid pulse rate and EKG changes-that although are not too dramatic-they should suggest myocarditis. Arrythmias are rare as a manifestation of myocarditis.

The patient was treated and in spite of therapy his condition became worse. He developed a gallop rhythm, the pulse rate became more rapid and he developed rales in the pulmonary fields. He was rapidly digitalized, the rales disappeared but he continued to be dyspneic with a rapid pulse and gallop rhythm. At the present time the pulse is still very rapid but he is not very dyspneic. He is receiving prednisone 150 mgs. a day in an effort to control his present myocarditis. I should like now to make a pause to let Dr. R. Díaz Bonnet discuss the roentgenological finding.

Dr. R. Díaz Bonnet: Chest film on March 7, 1966 (Fig. 5) : There is evidence of pleural reaction on the left obliterating

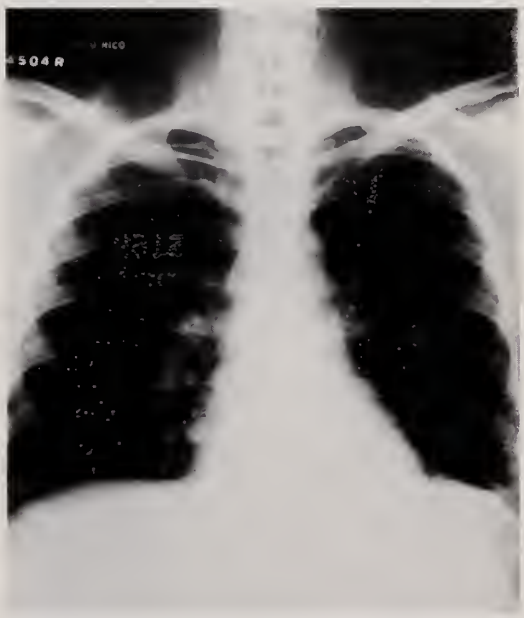


Fig. 5: Chest X-ray done on March 7, 1966.

the left costophrenic sulcus. There is a moderate collection of fluid at the mediastinopleural cavity in the left. The right costophrenic sulcus is flat. The visualized lung fields are clear. The heart and great vessels

are within normal limits. The size of the spleen cannot be determined in this film.

Re-examination of the chest on March 10, 1966 shows almost complete clearing of the pleural reaction. Minimal residual changes are demonstrated at the left lower hemithorax.

The examination of the chest on March 23 1966 shows evidence of interstitial thickening at the left base with associated haziness and nodular infiltration. The diaphragmatic leaf is elevated and there is evidence of a segmental atelectasis at the left lower lobe. Moderate pleural reaction is observed with collection of fluid at the left pleural cavity mainly at the inferior mediastino-pleural region. The cardiac silhouette is unchanged.

Film on May 30, 1966 (Fig. 6): There is noted haziness and an area of infiltration at the left infraclavicular region. Small radiolucencies are observed within this process. Disseminated interstitial thickening and infiltration is demonstrated at the right lung. There is evidence of segmental area of atelectasis at the right apical region. An area of pleuritic reaction is demonstrated at the left base. These is no significant change in the configuration of the cardiac silhoutte.

Film of June 13, 1966: There is noted a complete clearing of the process described on May 30, 1966 with no residual changes observed.

Film of August 9, 1966: (Fig. 7): There is noted an area of consolidation at the left upper lobe with moderate interstitial thickening at the left lower lobe and right base. Associated fine interstitial nodularities are demonstrated at these regions.



Fig. 6



Fig. 7

Thickening of the right middle low fissure is observed and minimal pleuritic reactions are demonstrated at the left base. The heart is increased in its transverse diameter when compared with the previous studies and there is straightening of the left border. The aorta is within the normal limits.

This case shows many of the radiographic features expected to be seen in the chest in acute lupus. You look for pleuritis, pneumonitis, carditis and splenomegaly. The pulmonary findings are the result of perivascular inflammation and are manifested by the widening of the pulmonary markings and the areas of interstitial pneumonia which are more frequently seen at the bases and sub-pleural bases. Minute to massive multiple hemorrhages may appear in the lungs secondary to necrosis of the walls of the small vessels. Sub-pleural areas of inflammation may occur which at times may obscure the cardiac shadow making the heart borders indistinct. Areas of segmental atelectasis may be present which may disappear completely. If complete remission occurs, all these findings may disappear completely or small areas of fibrous strands may be the sequela of this segmental atelectasis which are usually close to the pleura and also form tent-like adhesions. Secondary bacterial infections are not uncommon in acute lupus and they should be suspected when the upper lobes and the perihilar areas are involved or if there is a difuse pneumonitis. This case has shown that all these manifestations have cleared from time to time in periods of remission without residual changes.

The early finding in this case was that of pleural reaction which is the result of fibrinous inflammation and focal areas of necrosis which at a later stage may be followed by fibrosis and adhesions. Massive pleural effusion may occur but only in the early stages. Pleural effusion occurs in about 70% of the cases and it has been described bilaterally in as much of 50% of the cases.

Marked variation in the cardiac silhouette, the result of involvement of the heart either by endocarditis, myocarditis or pericarditis is an important finding in the radiographic diagnosis of acute lupus. This case shows in its late film a definite cardiac enlargement compatible with dilatation of the heart. To conclude, the diagnosis of systemic lupus should be considered in a radiograph of the chest in the presence of one or more of the above mentioned signs-pleuritis, pneumonitis, carditis or splenic enlargement.

Dr. Esther N. González: The laboratory, in the present admission, reveals that he has a hemoglobin of 7.2. He has always been anemic. In lupus, anemia is found in over 60% of all patients who have this disease. The anemia is normocytic, mormochromic and so far no etiologic factor for it has been found. It is well known that this anemia does not respond to the usual measures given for anemia such as folic acid, vitamin B_{12} or iron therapy. The anemia improves as the disease improves. When the patient with lupus gose into complete remission the hemoglobin becomes normal too. Occasionally patients with lupus develop another type of anemia, which is much less frequent, as it only occurs in about 5% of the cases, and this is acquired hemolytic anemia. Blood transfusions are not given because lupus patients are very allergic to

blood and they develop severe transfusion reaction. However, they are given when they are really needed and in acquired hemolytic anemia sometimes you are forced to give blood transfusions if the hemoglobin level drops too low.

The laboratory work in this patients is consistent with his present renal condition; a very high BUN, low total proteins. The total protein in this admission are not too low, but you must not forget that he received albumin infusions two weeks ago. Usually his albumin ran from 1.9 to 2 mg%. Uric acid is high, 8.7 mg%, but he is in renal failure. The latex was positive to 1:640 dilution. Latex fixation is positive in 20% of all patients with systemic lupus. L.E. cell preparation was positive (Fig. 2) and he had 3/ peripheral antinuclear antibody (Fig. 3). Antinuclear antibody are found in all patients with systemic lupus erythematosus. The fluorescent antinuclear antibody test thus is positive in all patients with this condition. Three patterns of nuclear fluorescence may be observed - diffuse, peripheral or speckled. The cluster of sphere pattern which was observed in our patient has not been described as yet in the literature. The antinuclear antibody test is not diagnostic for lupus, for it may be positive in about 30% of rheumatoid arthritis patients, but so far the peripheral pattern has been found only in patients with lupus. In March his antibody test was peripheral but by June it had changed to cluster of spheres (Fig. 4). Antinuclear antibodies belong to all three classes of inmunoglobulins IgG, IgM and IgA.

It is a well known fact that after antien stimulation the inmunoglobulin M increases and that about two weeks later the inmunoglobulin M level decreases and the inmunoglobulin G level increases. We wanted to find out if in systemic lupus there was any correlation between the inmunoglobulin class of antibody and the duration of the disease. We studied all patients, the ones who had a recent onset, and the ones in whom the duration of the disease was more than 10 years. And it was a surprise to find that patients who had a duration of the disease of less than one month, as well as those in whom the disease had been diagnosed 10 years or more, had difference in the level of inmunoglobulin G or inmunoglobulin M. The inmunoglobulin M was as high in those who had a recent onset as in those who had very prolonged disease. So from here we had to conclude that in lupus the antigenic stimulation that produces the inmunoglobulin class of antibody M or G persists throughout the duration of the disease of for prolonged periods of time.

As a final remark I would like to impress especially on the third year medical students that not all cases of lupus are as bad as the one presented here. At the present time in our Arthritis Clinic, in the University Hospital, we have about 50 patients with systemic lupus erythematosus. Of these 50 patients, about 10 patients are in complete remission receiving no steroid therapy. That is, they are getting only antimalarials or aspirin therapy to control their symptoms, and they are in complete remission because they are completely asymptomatic or with minimal activity with steroid therapy. Around 30 patients are either in complete remission or have minimal activity on steroid therapy. There is a third group that comprises about 8-10 pa-

tients who in spite of steroid therapy have moderate activity. None of them is as seriously ill as our patient, but they have moderate activity in spite of the fact that we are treating them with steroid and antimalarials.

Dr. Carlos Rubio: How could we differentiate between rheumatoid arthritis and systemic lupus - especially in those cases who started as rheumatoid arthritis - how do you tell later on whether they were not rheumatoid from the start and then developed lupus?
What is the basis of differentiation of both conditions?

Dr. Esther N. González: Lupus erythematosus and rheumatoid arthritis are two different condition not only clinically but inmunologically as well. Rheumatoid arthritis is limited to the joints, lupus erythematosus is a multisystem disease. You can not give the diagnosis of lupus unless you have a multisystem disease picture. Antinuclear antibodies are present in patients with lupus in 100% of the cases. Rheumatoid arthritis patients have only a 30% incidence of positive antinuclear antibody. You may have a rheumatoid arthritis patient with a positve L.E. cell preparation and yet you can not call it lupus unless they shows evidence of a multisystem disease. Family studies, which have been done in lupus patients as well as in rheumatoid arthritis patients have demostrated that the relatives of patients with rheumatoid arthritis have no abnormalities in the blood, while relatives of lupus erythematosus patients frequently show hyper-gammaglobulinemia. Patients with rheumatoid arthritis and positive LE cell have a 100% incidence of antinuclear antibody, so, although they are not called lupus from the start, they are considered a separate group and always are watched out for the appearence of a multisystem disease that then will be diagnostic of lupus erythematosus. In lupus erythematosus joint involvement is one of the most frequent manifestations. This joint involvement can exist for many years before the rest of the clinical picture appears. It is the same thing in some patients who develop only the skin condition and then years later develop the multisystem disease. They are patients with chronic discoid lupus who are diagnosed as such for many years until the rest of the clinical picture of systemic lupus appears.

Dr. Carlos Rubio: Is the prevalence of lupus and the course of these patients similar in the United States as in Puerto Rico?

Dr. Esther N. González: The course that these patients run in the Unites States is more or less the same as the one they run in Puerto Rico. Only that in the Unites States the incidence is greater in the spring when the sun starts to shine again after the winter time. Here in Puerto Rico the incidence is greater around the beginning of the fall.

Dr. Carlos Rubio: Why was Meticortelone given together with Metocorten when the two preparation are more or less the same?

Dr. Esther N. González: Meticortelone is almost the same as Meticorten, but many of these patients with lupus need a combination of drugs. We know that patients who have lupus sometimes respond better when you add to the therapy Meticortelone

intramuscular, so, because we have had this experience in previous patients we did it with this patient.

Dr. Lillian Haddock: What is the incidence of systemic lupus erythematosus in the Rheumatoid Arthritis Research Program in Guaynabo?

Dr. Esther N. González: Of 8,000 patients who have been screened in Guaynabo, over 3,000 have been examined. Of those 3,000 we have diagnosed 3 patients as systemic lupus. However, we can not say that is a true prevalence of lupus in a Puerto Rican Community because we have around 10 patients in the clinic who came from Cidra who have systemic lupus. So, we have to screen another population like the one from Cidra to compare the prevalence.

Dr. Roberto Rodríguez: How is the incidence of lupus in Puero Rico as compared with the United States?

Dr. Esther N. González: On the basis of the figures in Bellevue Hospital which is a hospital that drains a large community as compared to the number of patients referred to the University Hospital that receives referrals from 15 towns, I would say that we have more new cases coming every month than they do. But one can not be sure because an accurate statistical determination of new cases has not been done.

Dr. Norman Maldonado: What is your impression regarding the use of inmunosuppressive drugs in S L E ?

Dr. Esther N. González: Inmunosuppressive drugs have been tried in lupus by different investigators. At the begining it was thought, it was an impression at least, that they did not work because they were used in patients who were almost dead. Thus the drugs did not have a fair trial. However, while I was in the States I had the opportunity to follow several patients who were under inmunosuppressive agents. The experience was quite unsatisfactory because in the majority of the patients the drug had to be discontinued becase of the side - effects. There was one patient who died of a massive gastrointestinal hemorrhage. So, before using inmunosuppressive agents in our patients with lupus here in Puerto Rico I will wait until more favorable reports come in the literature.

Dr. Carlos Rubio: What is the value of a latex fixation in Puerto Rico?

Dr. Esther N. González: On the 3,000 patients who were examined in Guaynabo, 80% of those who had a positive latex did not had rheumatoid arthritis. However, we must admit that all these patients who came to Guaynabo complained of some sort of arthritis. So, we could not be sure whether some of them will in the long run develop rheumatoid arthritis. At present a control study is being done to determine what is the true incidence of the latex positive fixation in patient who have no complaints whatsoever of arthritis.

Dr. Ramón Suárez: What is the incidence now as compared to the incidence 25 years ago. It is my impression that now more patients are being diagnosed as lupus than they were 25 to 50 years ago. Will you claim any importance to the administration of penicillin, sulfa or any of the new drugs?

Dr. Esther N. González: Although the incidence of penicillin allergies, sulfa allergies and different allergies in patients with lupus is well established, we do not know

whether it is due to the fact that these patients are allergic to these medications to start with and it is not that the drugs are the precipitating factor in the onset of many of these lupus patients.

EDITORIAL

ON PHYSICAL DIAGNOSIS

The advent of sophisticated and frequently complicated machines, procedures and laboratory tests has greatly contributed to our progress in medicine. Quite unfortunately the young physician's thoughts are initially channelled in this direction at the expense of simple bedside techniques which are the cornerstone of the practice of medicine. The use of new equipment, laboratory test and procedures are not intended to supplant the history and physical examination but to offer the physician a choice of methods to confirm the diagnosis and improve the ways of treatment. These tests are selected after a good history and physical examination, keeping in mind that the reason for the selection is to seek an answer to a specific inquiry.

The art and science of examining a patient has not been well engraved in the minds of our young physicians. It is amazing how often they can quote the last scientific reports appearing on a journal and how can they fill the order sheets of laboratory and radiographic rejuests. It is depressing on the other hand, to observe how they can miss a diagnosis for not being able to hear a low frequency diastolic murmur, feel a spleen or fail to recognize a hypothyroid patient on inspection.

It is not easy to learn and more difficult to teach physical diagnosis. Quite often there are no precise measurements. It is wonderful to observe how a well-trained physician with rather crude measurements can achieve such a high degree of precision in diagnosis. The fact that the methods in physical examination have their limitations should not be used as an excuse for not knowing and utilizing well their capabilities. These techniques are always carried by the physician wherever he goes and are always available for him to be used at any time.

The teaching of acoustic diagnosis requires a long time. A physician has no accurate way to measure intensity of sounds generated within the body or produced by external stimulus (percussion). The student must be taught by personal instruction and he must learn to judge the intensity of sounds by actual practice and as being told by his teachers. He must learn to train his ears and judgement according to the patterns of his instructors. The mental measurement of time intervals is difficult to grasp. The use of electromechanical registers, such

as the phonocardiograph, will help the student to develop a concept of time intervals. In the process of teaching one must stress that the phonocardiograph is not a substitute for the sthetoscope. I haven't yet seen a physician walking with a phonocardiograph in his pocket.

In the process of teaching physical diagnosis the instructor must describe in wards the acoustic phenomena and correlate the finding with the physiology of the organ, either normal or abnormal. At times the instructor, though being able to recognize the findings, lacks the vocabulary to describe it and remains mute or diplomatically avoids an answer when asked about the description of a sound. Sound must be described to the students according to such physical parameters as location, intensity, duration, quality and frequency. Unfortunately the term quality of sound has two connotationss one pertaining to characteristic overtones and another refering to intensity when describing heart sounds.

The physical examination of the lungs have been gradually neglected and its value involved in a sutile and sterile polemic against the roentgenologic examination of the chest. When the patient gets a chest X-ray on admission, it is interesting to observe hoy cursory the physical examination of the chest is at times performed, as if guarding its appearance. Certainly, one must remember the assets and the limitations of both procedures.

It seems to me that the main problem in the training of physicians is that they are not taught how to examine the patients well. At times the diagnosis is missed because clear findings are not seen, heard or palpated. To fill this gap there is a compensatory tendency to order more diagnostic studies and consultations without a clear orientation. Every phisician must concentrate in performing a good physical examination and remember that every time a short-cut is taken something will be missed sooner a later. The physical examination is a personal service to the patient and it should be performed in a masterful way, proper of a physician.

Francisco Ramos Morales, M.D.

NOTICIAS

Locales

CONGRESOS Y CONFERENCIAS

Octubre 6-8 — Convención de la Sección de Psiquiatría, Neurología y Neurocirugía, en el anfiteatro de la Asociación Médica de Puerto Rico y los hoteles San Juan y Americana.

Octubre 17-21 — Congreso de Cirujanos Neurológicos en el Hotel Americana. Este Congreso es auspiciado por un grupo de médicos norteamericanos visitantes.

Octubre 19 — Conferencia sobre Neurología y Neurocirugía por el Profesor Dubean en la Asociación Médica de Puerto Rico.

Octubre 28-29 — Asamblea Anual del American College of Physicians en la Asociación Médica de Puerto Rico. Para información favor de llamar al Dr. José A. De Jesús.

Octubre 31 — Conferencia por el Dr. Alfred M. Bongiovanni sobre Enfermedades de la Tiroide en la Asociación Médica de Puerto Rico. Esta Conferencia es auspiciada por la Sección de Pediatría de la Asociación Médica de Puerto Rico.

Octubre 31-Nov. 2 — Conferencias por el Dr. Henry A. Marriott en la Asociación Médica de Puerto Rico. Estas conferencias están auspiciadas por la Sección de Medicina Interna y Cardiología y el Comité de Cursos Post-Graduados de la Asociación Médica de Puerto Rico.

Octubre 31-Nov. 3 — Convención Anual de la Sociedad de Medicina Tropical e Higiene en el Hotel Americana.

Noviembre 15-19 — Asamblea Anual de la Asociación Médica de Puerto Rico en el Hotel San Juan.

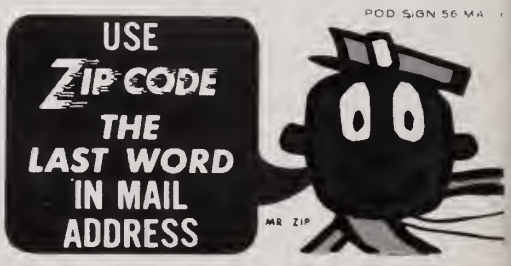
Noviembre 21-25 — Conferencia por el Dr. Albert Montgomery Kligman auspiciada por el "American Academy of General Practice" y la Sección de Medicina General de la AMPR, en los salones de la Asociación Médica de Puerto Rico.

Diciembre 2 — Conferencia sobre el Dr. Bailey K. Ashford en la Escuela de Medicina.

AMERICAN COLLEGE OF SURGEONS

En la última reunión del American College of Surgeons, celebrada el 13 de octubre de 1966 en California, fueron iniciados como "Fellows" de esa organización los siguientes compañeros médicos:

Nelson Cortés
José L. Iturrino
José R. Pérez-Anzalota
Manuel Fernández-Durán
Leovigildo Cuello
Guillermo E. Aragón
Luis A. Díaz Bonnet
José F. Bernal-Rosa



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Efectivo el 1 de enero de 1967 es mandatorio incluir el número de zona postal en todas las di-

recciones. Aquéllas que no lo tengan no recibirán el Boletín.

Agradeceremos, por lo tanto, a nuestros corresponsales de quienes no tenemos su número de zona postal, nos lo suministren para completar sus direcciones, de manera que puedan seguir recibiendo el Boletín de enero próximo en adelante.

Nacionales

Nov. 7-9 — Annual Meeting of the Association of Military Surgeons of the United States, to be held at the Washington Hilton, Washington, D.C.

Dec. 12-14 — National Conference on Air Pollution, in Washington, D.C.

Jan. 16-20, 1967 — Basic Mechanisms of Renal Disease, at Cornell University Medical Center, and New York Hospital, New York, N.Y.

Jan. 22-23 — The Council on Medical Service and the Division of Socio-Economic Activities of the American Medical Association will sponsor the First National Congress on Socio-Economics of Health Care at the Palmer House in Chicago, held at Fontainebleau Hotel, Miami Beach.

Jan. 23-27 — Current concepts in Blood Disease, University of Miami School of Medicine.

Jan. 30-Feb. 3 — Newer Aspects of Experimental and Clinical Allergy, held at the Sheraton-Boston Hotel, Boston, Mass.

Feb. 6-10 — Biochemical Lesions in Internal Medicine, Washington University School of Medicine, St. Louis, Mo.

April 3-7 — Gill Memorial Eye, Ear and Throat Hospital announces to the Profession the Fortieth Annual Spring Congress in Ophthalmology and Otolaryngology.

ANUNCIOS

PHYSICIANS WANTED

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Instrucciones para los Autores:

El Boletín acepta para su publicación artículos relativos a medicina y cirugía y las ciencias afines. Igualmente acepta artículos especiales y correspondencia que pudiera ser de interés general para la profesión médica.

El artículo, si se aceptara, será con la condición de que se publicará únicamente en esta revista.

Para facilitar la labor de revisión de la Junta Editora y del impresor, se requiere de los autores que sigan las siguientes instrucciones:

a) Los trabajos deberán estar escritos a máquina a doble espacio y por un solo lado de cada página, en duplicado y con amplio margen.

b) En página separada debe incluirse lo siguiente: título (no excediendo de 80 letras y espacios), nombre del autor (es), institución y dirección postal del autor.

c) Artículos referentes a resultados de estudios clínicos o investigaciones de laboratorio deben organizarse bajo los siguientes encabezamientos: (1) introducción, (2) material y métodos, (3) resultados, (4) discusión, (5) resumen (en español e inglés), y (6) referencias.

d) Artículos referentes a estudios de casos aislados deben organizarse en la siguiente forma: (1) introducción, (2) observaciones del caso, (3) discusión, (4) resumen (en español e inglés), (5) referencias.

e) Las tablas, notas al calce y leyendas deben aparecer en hojas separadas.

f) Si un artículo ha sido leído en alguna reunión o congreso, así debe hacerse constar como una nota al calce.

g) Deben usarse los nombres genéricos de los medicamentos. Podrán usarse también los nombres comerciales, entre paréntesis, si así se desea.

h) Se usará con preferencia el sistema métrico de pesos y medidas.

i) Las fotografías y microfotografías se someterán como copias en papel de lustre sin montar. Los dibujos y gráficas deben prepararse a tinta negra y en papel blanco. Todas las ilustraciones deben estar numeradas (números arábigos) e indicar la parte superior de las mismas. Debe escribirse una leyenda para cada ilustración.

j) Las referencias deben ser numeradas sucesivamente de acuerdo con su aparición en el texto. Los siguientes ejemplos pueden servir de modelo:

6. *Koppisch, E.* Pathology of arteriosclerosis. Bol. Asoc. Med. P. Rico 46: 505, 1954. (artículo de revista).
4. *Wintrobe, M. M.* Clinical Hematology, 3rd Ed. Lea and Febiger, Philadelphia, 1952, p. 67. (libro).

Deben usarse solamente las abreviaturas indicadas en el Cumulative Index Medicus que publica la Asociación Médica Americana.

Instructions to Authors:

The Boletín will accept for publication contributions relating to the various areas of medicine surgery and allied medical sciences. Special articles and correspondence on subjects of general interest to physicians will also be accepted. All material is accepted with the understanding that it is to be published solely in this journal.

In order to facilitate review of the article by the Editorial Board and the work of the printer, the authors must conform with the following instructions:

a) The entire manuscript, including legends and references, should be typewritten double-spaced in duplicate with ample margins.

b) A separate title page should include the following: title (not to exceed 80 characters and spaces), author's name (s); institution, and author's mailing address.

c) Articles reporting the results of clinical studies or laboratory investigation should be

organized under the following headings: (1) introduction, (2) material and methods, (3) results, (4) discussion, (5) summary in English and Spanish, (6) references.

d) Case reports will include (1) introduction, (2) description of the case, (3) discussion, (4) summary in English and Spanish, (5) references.

e) Tables, footnotes and legends to figures should appear in separate sheets.

f) If the paper has been presented at a meeting, the place and date should be stated as a footnote.

g) Generic names of drugs should be used. Trade names may also be given in parenthesis, if desired.

h) Metric units of measurement should be used preferentially.

i) Photographs and photomicrographs should be submitted as glossy prints, unmounted. Drawings and graphs should be made in black ink on white paper. All illustrations should be numbered (Arabic) and the top indicated. A legend should be given for each.

j) References should be numbered serially as they appear in the text. The following form will be used:

6. *Koppisch, E.* Pathology of arteriosclerosis. Bol. Asoc. Med. P. Rico 46: 505, 1954. (for journal articles).
4. *Wintrobe, M. M.* Clinical Hematology, 3rd Ed. Lea and Febiger, Philadelphia, 1952, p. 67, (for books).

Abreviations will conform to those used in the Cumulative Index Medicus, published by the American Medical Association.



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Before prescribing or administering, read product circular with package or available on request.

1. Brest, A. N.: Hemodynamic response to antihypertensive drug therapy, J.A.M.A. 192:127-130, April 15, 1965.

2. Onesti, G. et al.: Comparative hemodynamic effects of antihypertensive agents: alpha-methyl-dopa, pargyline and isocaramidine. Abstracts of the 37th Scientific Sessions and 18th Annual Meeting, Council on Arteriosclerosis, American Heart Association, Atlantic City, October 21-22, 1964. Circulation 30:III-135-III-136, October 1964.

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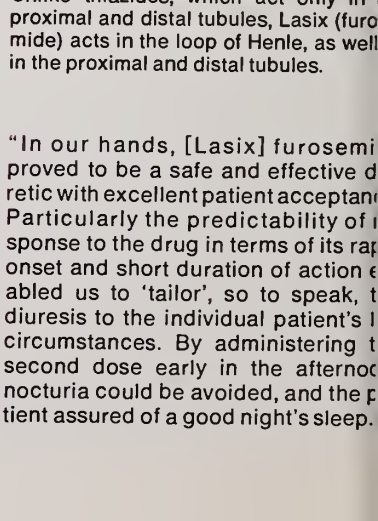
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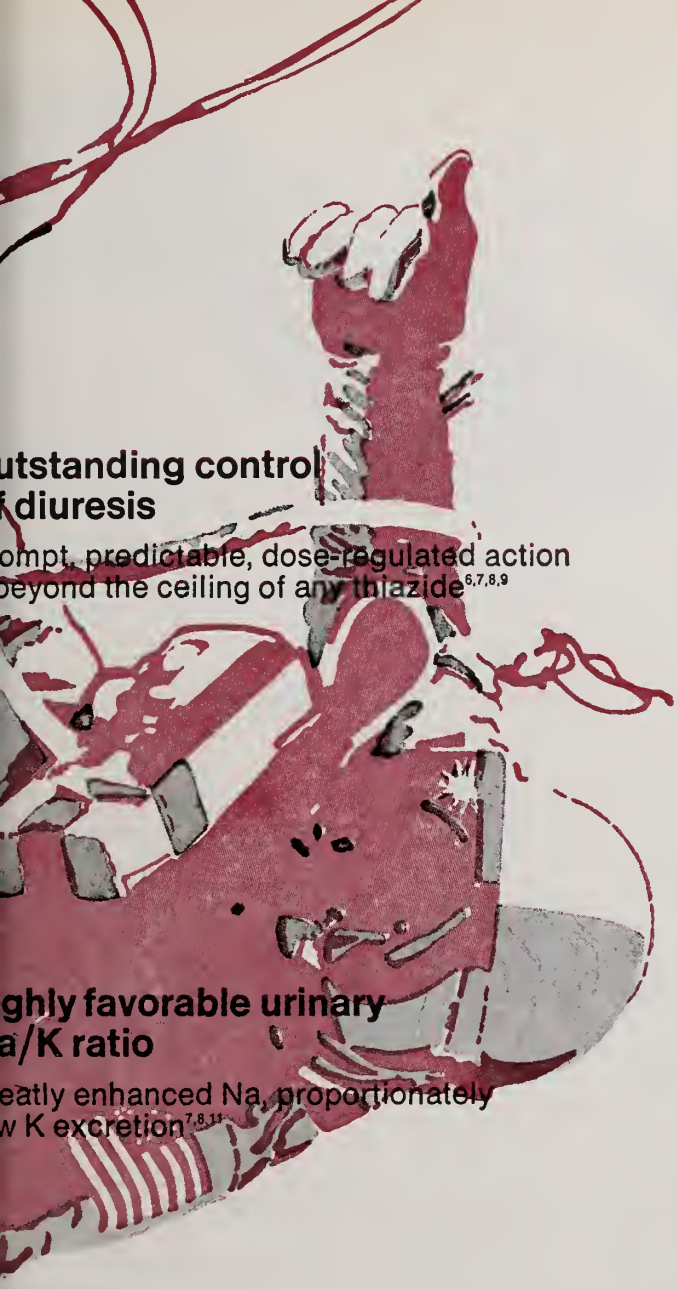
efficacy

beyond the capacity of any thiazide—outperforms the thiazides by acting throughout the nephron[2,3,4,5]

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no more "round-the-clock" diuresis[6,7,8,9,10]

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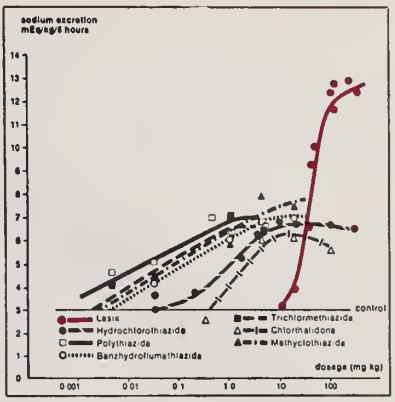
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beyond the ceiling of any thiazide[6,7,8,9]

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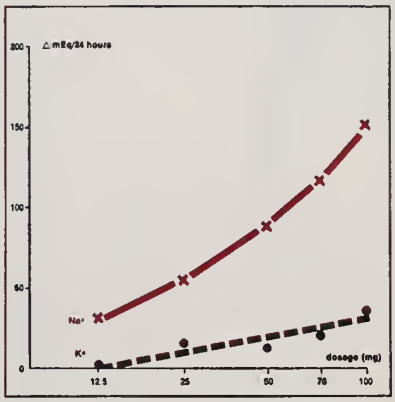
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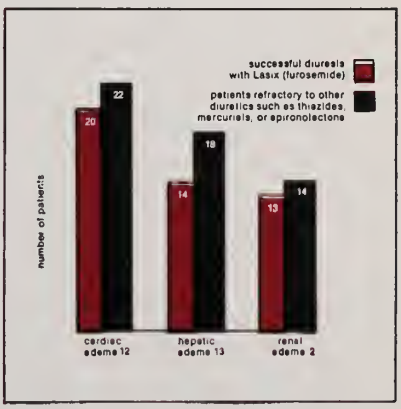
cardiac, hepatic, and renal edema, including
iazide-refractory cases[2,12,13]



The natriuretic action of Lasix (furosemide) in rats compared with that of various other diuretics (after Timmerman, *et al.*[6])



Dose-response curve on sodium and potassium excretion in normal subjects after oral administration of Lasix (furosemide) (after Kleinfelder[8])



Response to Lasix (furosemide) in patients refractory to other diuretic agents: results from three studies[2,12,13]

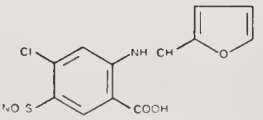
Space photograph courtesy of the National Aeronautics and Space Administration.

Lasix® brand of furosemide

WARNING—Lasix (furosemide) is a new, potent diuretic, which if given in excessive amounts can lead to a profound diuresis with water and electrolyte depletion. Therefore, careful medical supervision is required and dose and dose schedule have to be adjusted to the individual patient's needs. (See under "Dosage and Administration.")

Lasix (furosemide) is a new diuretic, chemically distinct from the organomercurials, thiazides and other heterocyclic compounds. It is characterized by: a high degree of efficacy; a rapid onset of action; a comparatively short duration of action; a ratio of minimum to maximum effective dose higher than 1.10; the fact that it acts not only at the proximal and distal tubule but also at the ascending limb of Henle's loop.

Chemistry—Lasix (furosemide) is an anthranilic acid derivative. Chemically, it is 4-chloro-N-furfuryl-5-sulfamoylanthranilic acid. The structural formula is as follows:



Indications—Lasix (furosemide) is indicated for the treatment of edema associated with congestive heart failure, cirrhosis of the liver, and renal disease, including the nephrotic syndrome. Lasix (furosemide) is particularly useful when an agent with greater diuretic potential than those commonly employed is desired. Until further clinical experience is accumulated, Lasix (furosemide) is not recommended for use in hypertension.

Dosage and Administration—The usual dose of Lasix (furosemide) is 1 to 2 tablets (40 to 80 mg) given as a single dose, preferably in the morning. Ordinarily, a prompt diuresis ensues. Depending on the patient's response, a second dose can be administered 6 to 8 hours later. This dosage and dosage schedule can then be maintained or even reduced. If the diuretic response with a single dose of 1 to 2 tablets (40 to 80 mg) is not satisfactory, e.g., in a patient with congestive heart failure refractory to maximal doses of thiazides, the following schedule should be used: Increase this dose by increments of 1 tablet (40 mg) not sooner than 6 to 8 hours after the previous dose until the desired diuretic effect has been obtained. This individually determined single dose should then be given once or twice daily (e.g., at 8:00 a.m. and 2:00 p.m.). Based on completed studies, a maximum daily dose of 200 mg should not be exceeded. Higher doses are currently under investigation. The mobilization of edema may be most efficiently and safely accomplished by utilizing an intermittent dosage schedule in which the diuretic is given for 2 to 4 consecutive days each week. With doses exceeding 80 mg/day and given for prolonged periods, careful clinical and laboratory observations are particularly advisable. Until further experience in children is accumulated, Lasix (furosemide) should not be given to children.

Contraindications—Lasix (furosemide) is contraindicated in anuria. If increasing azotemia and oliguria occur during treatment of severe progressive renal disease the drug should be discontinued. In hepatic coma and in states of electrolyte depletion, therapy should not be instituted until the basic condition is improved or corrected. Lasix (furosemide) is contraindicated in patients with a history of hypersensitivity to this compound.

Supplementary Warnings—Excessive diuresis may result in dehydration and reduction in blood volume, with circulatory collapse and with the possibility of vascular thrombosis and embolism particularly in elderly patients. Excessive loss of potassium in patients receiving digitalis glycosides may precipitate digitalis toxicity. Care should also be exercised in patients receiving potassium depleting steroids. Frequent serum electrolyte, CO_2, and BUN determinations should be performed during the first few months of therapy and periodically thereafter and abnormalities corrected or the drug temporarily withdrawn. **In patients with hepatic cirrhosis and ascites initiation of therapy with Lasix (furosemide) is best carried out in the hospital.** Sudden alterations of fluid and electrolyte balance in patients with cirrhosis may precipitate hepatic coma; therefore, strict observation is necessary during the period of diuresis. Supplemental potassium chloride and, if required, an aldosterone antagonist are helpful in preventing hypokalemia and metabolic alkalosis. As with any new drug, patients should be observed regularly for the possible occurrence of blood dyscrasias, liver damage, or other idiosyncratic reactions. In those instances where potassium supplementation is required, coated potassium tablets should be used only when adequate dietary supplementation is not practical. There have been several reports, published and unpublished, concerning nonspecific small bowel lesions consisting of stenosis with or without ulceration, associated with the administration of enteric-coated thiazides with potassium salts. These lesions may occur with enteric-coated potassium tablets alone or when they are used with non-enteric-coated thiazides, or certain other oral diuretics. These small bowel lesions have caused obstruction, hemorrhage, and perforation. Surgery was frequently required, and deaths have occurred. Based on a large survey of physicians and hospitals, both American and foreign, the incidence of these lesions is low, and a causal relationship in man has not been definitely established. Available information tends to implicate enteric-coated potassium salts although lesions of this type also occur spontaneously. Therefore, coated potassium-containing formulations should be administered only when indicated, and should be discontinued immediately if abdominal pain, distention, nausea, vomiting, or gastrointestinal bleeding occur.

Usage in Pregnancy—The use of any drug in pregnancy, lactation or in the childbearing age group requires that the potential benefits of the drug be weighed against possible hazards to the mother and child. Reproduction studies with Lasix (furosemide) in mice, rabbits, and rats have produced no evidence of drug-induced fetal abnormalities. However, Lasix (furosemide) has had only limited use in pregnant patients.

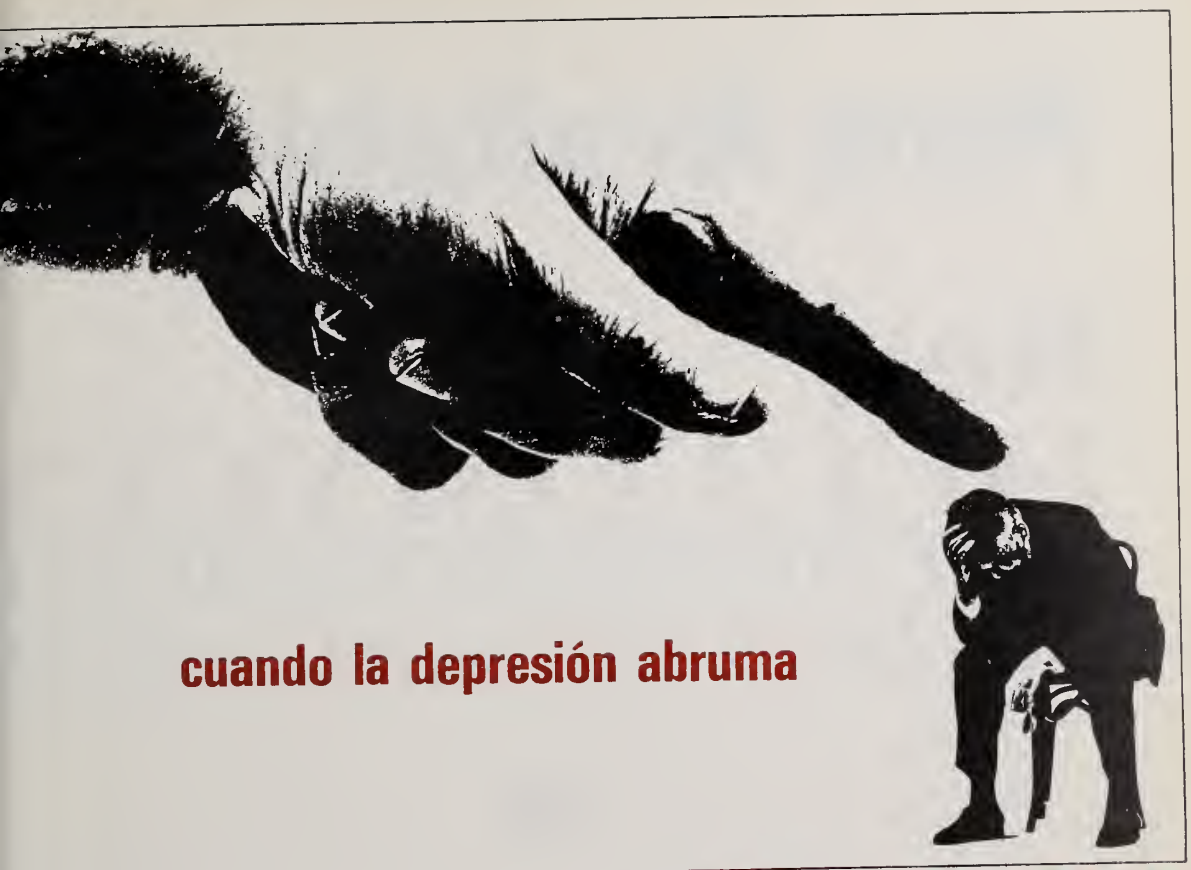
Precautions—As with any potent diuretic, electrolyte depletion may occur during therapy with Lasix (furosemide), especially in patients receiving higher doses and a restricted salt intake. Electrolyte depletion may manifest itself by weakness, dizziness, lethargy, leg cramps, anorexia, vomiting, and/or mental confusion. In edematous hypertensive patients being treated with antihypertensive agents, care should be taken to reduce the dose of these drugs when Lasix (furosemide) is administered, since Lasix (furosemide) potentiates the hypotensive effect of antihypertensive medications. Asymptomatic hyperuricemia can occur and gout may rarely be precipitated. Reversible elevations of BUN may be seen. These have been observed in association with dehydration which should be avoided, particularly in patients with renal insufficiency. Although no pronounced effect on carbohydrate metabolism has been demonstrated, periodic checks on urine and blood glucose should be made in diabetic patients receiving Lasix (furosemide). Occasional increases in blood glucose have occurred during therapy with Lasix (furosemide). Sulfonamide diuretics have been reported to decrease arterial responsiveness to pressor amines and to enhance the effect of tubocurarine. Great caution should be exercised in administering curare or its derivatives to patients undergoing therapy with Lasix (furosemide), and it is advisable to discontinue Lasix (furosemide) for one week prior to any elective surgery.

Adverse Reactions—Infrequent skin rash, pruritus, paresthesia, blurring of vision, postural hypotension, nausea, vomiting, or diarrhea may occur. A single case of thrombocytopenia has been reported in which Lasix (furosemide) was considered to be the causative agent. There have been a few instances of leukopenia and one report of acute pancreatitis although relationship to the drug has not been established. Lasix (furosemide) induced diuresis has occasionally been accompanied by weakness, fatigue, lightheadedness or dizziness, muscle cramps, thirst, and urinary frequency.

How Supplied—Lasix (furosemide) is supplied as white, monogrammed, scored tablets of 40 mg in amber bottles of 100.

References: (1) Kerr, D. N. S., and Robson, A. O.: Practitioner *194*:694, 1965. (2) Muth, R. G.: J.A.M.A. *195*:1066, 1966. (3) Suki, W.; Rector, F. C., Jr., and Seldin, D. W.: J. Clin. Invest. *44*:1458, 1965. (4) Deetjen, P.: Pflüger's Arch. ges. Physiol. *284*:184, 1965. (5) Malnic, G.; Vieira, F. L., and Enokibara, H.: Nature *208*:80, 1965. (6) Timmerman, R. J.; Springman, F. R., and Thoms, R. K.: Current Therap. Res. *6*:88, 1964. (7) Hutcheon, D. E.; Mehta, D., and Romano, A.: Arch. Int. Med. *115*:542, 1965. (8) Kleinfelder, H.: Deutsche med. Wchnschr. *8*:459, 1963. (9) Stokes, W., and Nunn, L. C. A.: Brit. M. J. *2*:910, 1964. (10) Atkins, L. L.: Geriatrics, in press. (11) Verel, D.; Stentiford, N. H.; Rahman, F., and Saynor, R.: Lancet *2*:1088, 1964. (12) Peltola, P.: Acta med. scandinav. *177*:777, 1965. (13) Steigmann, F.; Oz, R., and Dubin, A.: Am. J. M. Sc., in press.

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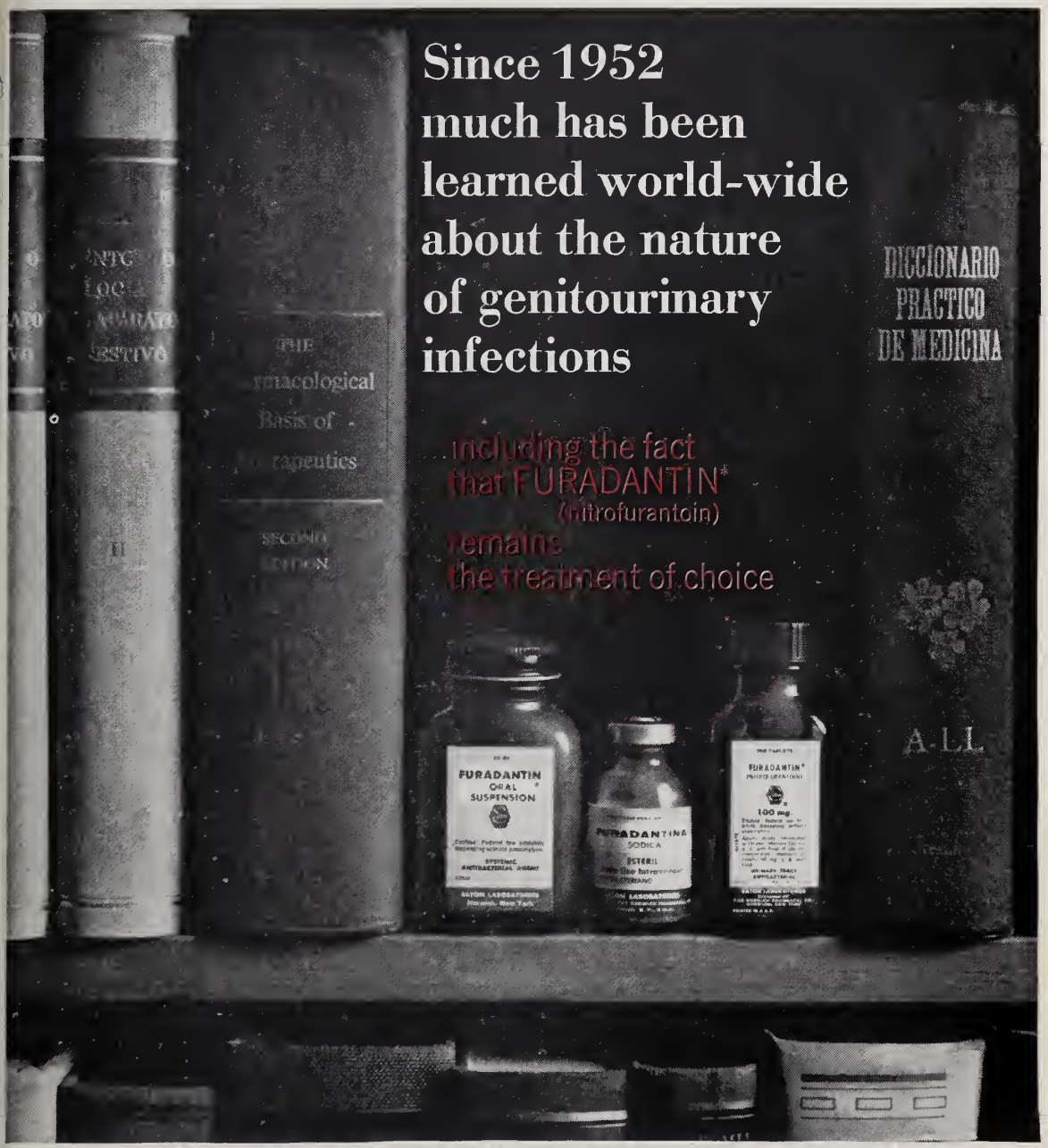
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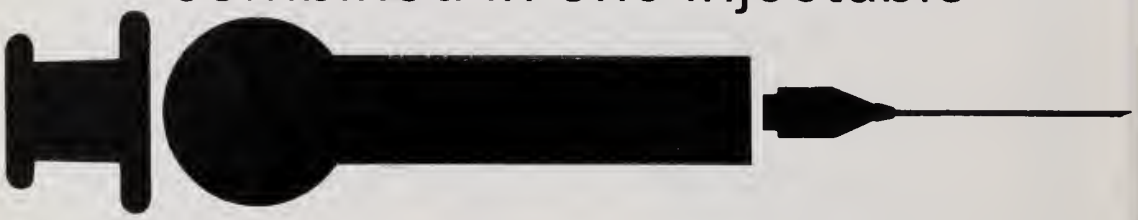
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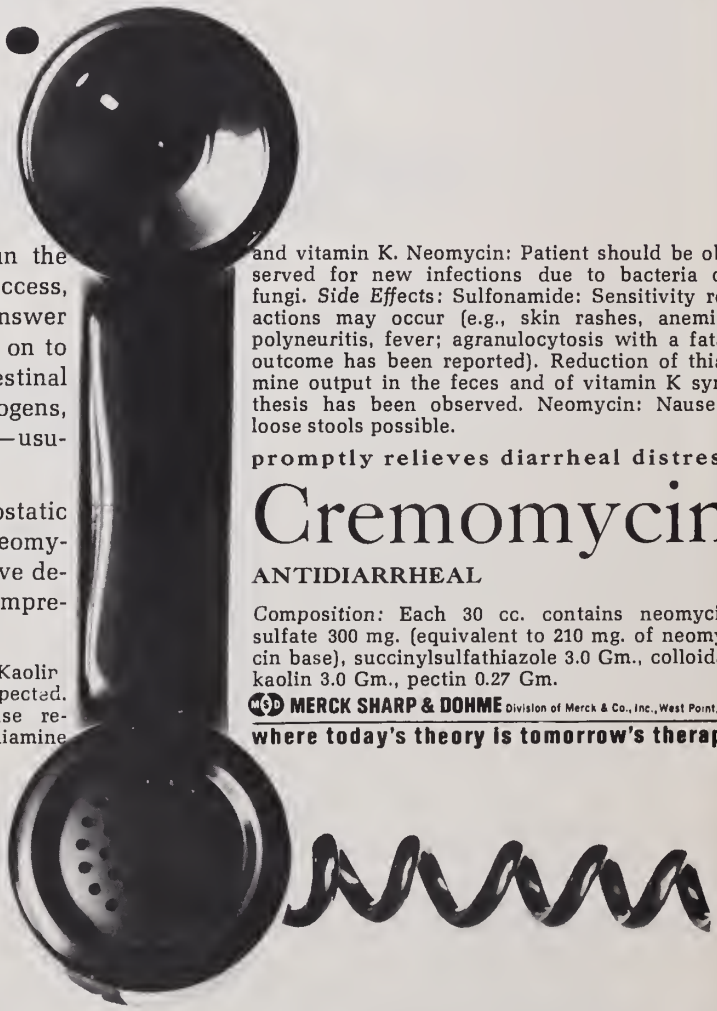
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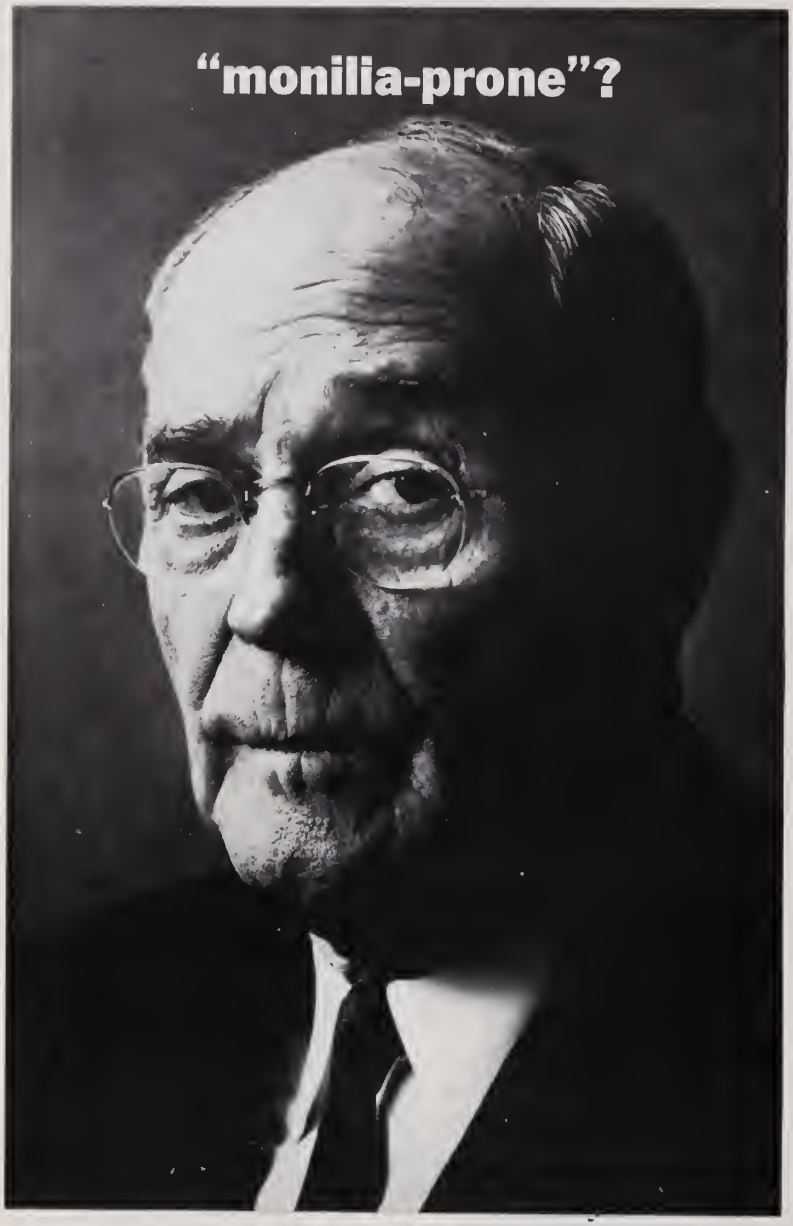
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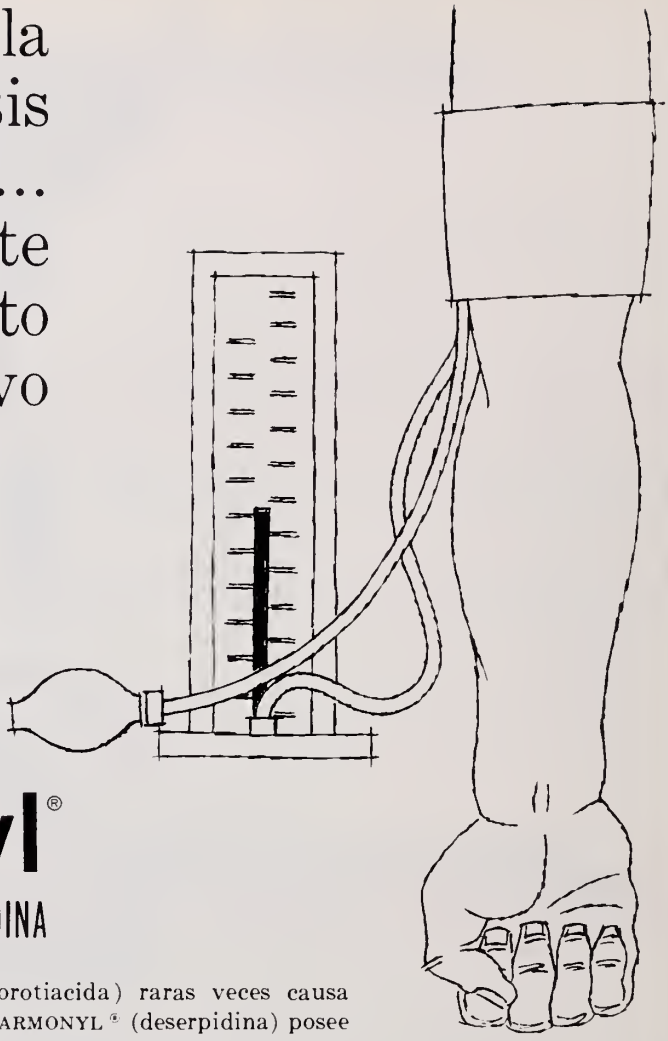


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PYURIA IN ACUTE INFANTILE DIARRHEA

O. González Alvarez, M. D.

Pyuria is said to indicate the presence of a urinary infection. However, we all realize that the urine of infants suffering from acute diarrhea is frequently reported as showing leukocytes. Is this infection of the urinary tract? Is this contamination? Shall we treat these infants? A clear answer to these questions is of practical value in our country where acute gastroenteritis is still a leading cause of death during early infancy. Adequate treatment of a urinary tract infection if present, will help the infant recover besides avoiding the possibility of an untreated pyelonephritis progressing into a chronic phase. It is the purpose of the present investigation to compare routinely collected urine samples with samples collected in a plastic bag after careful cleansing of the genital area as to the incidence of pyuria and bacteriuria.

Materials and Methods

288 infants admitted to our acute diarrhea ward had their urine collected by the plastic bag method as soon as possible after admission. All were considered to be either moderately or severely dehydrated. In 100 cases paired urine samples collected at an interval not over six hours but usually much shorter were available for comparison. Close to 100 other infants were used for tabulating the results of routinely collected urine samples. Thirty infants admitted to our surgical ward served as controls. Infants treated with antibiotics prior to admission were not excluded from the study. All the clean voided urine specimens collected in plastic bags were obtained by the same graduate nurse. Without delay she would take the sample over to the laboratory where the same technician processed it. In all cases urinalysis and colony counts were performed within two hours after collection.

Clean voided specimens were collected following the procedure outlined by Pryles (1). The perineum and vulva in the females and the prepuce and glans penis in the males (after as much retraction of the prepuce as possible) were carefully scrubbed with hexachlorophene (pHisoHex) for about one minute. Aqueous benzalkonium (Zephiran) 1:1,000 was then applied using only single strokes with a fresh cotton swab for each stroke. After the area was dry a plastic bag (Sterilon Pediatric urine collector) was firmly applied keeping the anus out. The nurse observed the infant at least every 30 minutes for urination. If a stool was passed while the plastic bag was in place, the whole procedure was repeated and a new bag applied, Complete urinalysis was performed. A colony count was done using a calibrated platinum inoculating loop which supplied 1/1000 of 1 ml. Both blood agar and MacConkey media plates were inoculated. Ater incubation for 24 hours colonies were counted and cultures performed in those with counts over 100,000.

From the Department of Pediatrics of the San Juan City Hospital. This study was supported by the U.S. Army Research Grant on Metabolic Studies in Sprue Patients conducted by the University of Puerto Rico School of Medicine.

Presented in part at the annual meeting of the Puerto Rico Medical Association on November 1965.

Results

Males predominated in the sample studied in a ratio of 1.6 to 1.0. There were no circumcised males. Whites predominated in a ratio of 5.6 to 1.0. Prematures constituted 20% of the sample studied.

71% of our patients were under four months of age (Table I).

TABLE I: AGE DISTRIBUTION OF 365 INFANTS STUDIED

Age	Percentage
30 days or under	21.4
31 - 60	28.1
61 - 90	12.7
91 - 120	8.9
121 - 150	7.3
151 - 180	7.3
180 and over	14.0

Note: 71% subjects are under four (4) months of age.

We compared routinely collected samples, that is, those samples collected by the nurse on duty with the clean voided samples collected in plastic bags as to the incidence of pyuria. Arbitrarily, though selected after careful analysis of the published data (2), five or more leukocytes per high power field in the centrifuged sediment defined pyuria. Our data is shown in Table II. Pyuria was reduced from 38% to 14% just by employing a better but still simple method of collection.

Table III presents our findings regarding the incidence of pyuria in routinely collected samples and the sex of the patient. There is no striking difference between male and female infants. The same appears to be true with regards to the clean voided samples as demonstrated in Table IV.

Duplicate urine samples are shown in Table V. Both samples show pyuria in six cases out of one hundred. Both samples without pyuria in 57 cases out of 100. A correlation of only 63%.

A breakdown of the clean voided samples collected in plastic bags show 244 with 4 or less white blood cells per high power field.

TABLE II: *PYURIA IN INFANTS BELOW 1 YR. OF AGE WITH ACUTE GASTROENTERITIS

	# Cases	%
Routine Urine Collection	385	100%
With Pyuria	147	38.1
Plastic Bag Collection	288	100
With Pyuria	41	14.2

**Pyuria defined as 5 or more W.B.C./H.P.F. sediment.*

TABLE III: PERCENTAGE OF ROUTINE URINE SAMPLES WITH PYURIA AS RELATED TO SEX

Samples acc. to sex	Number	%
Total	385	100
With Pyuria	147	38.1
Males (uncircumcised)	219	100
With Pyuria	89	40.6
Females	166	100
With Pyuria	58	34.9

TABLE IV: PERCENTAGE OF PLASTIC BAG URINE COLLECTIONS WITH PYURIA AS RELATED TO SEX

Samples acc. to sex	Number	%
Total	288	100
With Pyuria	41	14.2
Males (uncircumcised)	156	100
With Pyuria	30	19.2
Females	91	100
With Pyuria	11	12.0

TABLE V: COMPARISON OF RESULTS IN 100 INFANTS WITH ACUTE GASTROENTERITIS IN DUPLICATE URINE SAMPLES

Routine and plastic bag collection		
Both samples with Pyuria	6%	63%*
Both samples without Pyuria	57%	
Routine pos. and plastic bag negative	26%	
Plastic bag pos. and routine negative	11%	
	100%	

**Poor correlation.*

15 cases (6%) of these had bacterial colony counts of 100,000 or over. 12 had positive cultures. 68 cases (27.8 percent) had counts between 1,000 — 10,000 and another 54 cases (22%) had counts between 10 — 100,000. Data shown in Table VI.

TABLE VI: COMPARISON OF COLONY COUNTS IN CASES WITH 0-4 CELLS IN URINE COLLECTION IN PLASTIC BAGS

Colony Count	# Cases	%
0	92	37.7
1 - 1,000	15	6.1
1,001 - 10,000	68	27.8
10,001 - 100,000	54	22.1
Over 100,000	15*	6.1
Total	244	99.8%

**15 cultured; 12 positive.*

In the group of cases with pyuria (40 cases), 36 cases (90%) had counts over 10,000. 23 cases (57.5%) had bacterial counts over 100,000. Of these, 20 could be cultured and all were positive, (Table VII). Out of sheer curiosity, I classified the cases according to Stansfeld's (3) criteria for pyuria, that is, 10 cells per high power field. The results shown in Table VIII demonstrate that out of 26 cases 23 (88.3%) had counts over 10,000 but the percentage of cases with counts over 100,000 rose to 73%.

Table IX shows the incidence of urinary infection in relation to bacterial isolations in

TABLE VII: COMPARISON OF COLONY COUNTS IN CASES WITH 5 CELLS OR MORE IN URINE COLLECTION IN PLASTIC BAGS

Colony Count	# Cases	%
0	2	5
1 - 1,000	0	0
1,0001 - 10,000	2	5
10,001 - 100,000	13	32.5
Over 100,000	23*	57.5
Total	40	100.0%

**20 cases cultured; all positive.*

TABLE VIII: COMPARISON OF COLONY COUNTS IN CASES WITH 10 CELLS OR MORE IN URINE COLLECTION IN PLASTIC BAGS

Colony Count	# Cases	%
0	2	7.7
1 - 1,000	0	0
1,001 - 10,000	1	3.8
10,001 - 100,00	4	15.3
Over 100,00	19 (note)	73.0
Total	26	99.8%

Note: 20 cases cultured; 18 positive.

TABLE IX: INCIDENCE OF URINARY INFECTION IN RELATION TO BACTERIAL ISOLATIONS IN STOOLS

	Number	%
Total samples	222	100
With urinary infection	37	16.7
Pos. Stool Isolation	65	100
With urinary infection	9	13.8
Neg. Stool Isolation	157	100
With urinary infection	28	17.9

the stools. There is not a higher association between specific enteriditis and increased incidence of urinary infection.

Prior antibiotic therapy which in about two thirds of those treated consisted of neomycin failed to affect the incidence of urinary infection.

79% of the urine cultures show Esch. coli either alone or in combination with enterococci. Proteus and Klebsiella were also isolated.

Both urine and stool were positive for Esch. coli in 12 of 76 cases (15.7%) with positive isolations for Esch. coli enteropathogenic. No typing of the Esch. coli isolated from the urine was performed, so the significance, if any of this finding, could not be established.

Fever and a white blood cell count of over 10,000 in peripheral blood as well as predominance of neutrophiles in the differential count were not helpful as indices pointing to the presence of urinary infection in this group of patients with acute gastroenteritis.

30 infants admitted to our surgical unit served as controls. 27 (90%) show 4 or less white blood cells per high power field. Of the three with pyuria one was lost to follow-up. The second was a case of pyloric stenosis

TABLE X: EFFECT OF PRIOR ANTIBIOTIC* TREATMENT

	Number	%
Total Samples	222	100.0
Pos. Stool Isolation	65	29.3
With Urinary Infection	37	16.7
Prior antibiotic Rx	115	100.0
Pos. Stool Isolation	26	22.6
With Urinary Infection	16	13.8

**Neomycin in 2/3.*

after surgery was performed. The third case was that of a fractured femur. They showed 5 and 10 white blood cells respectively and the pyloric stenosis grew 17,000 colonies of enterococci.

Discussion

The diagnosis of infection of the urinary tract is difficult in infants with diarrhea as pyuria is often present under these circumstances (4). The quantitative examination of a carefully collected urine specimen is most important in arriving at this diagnosis. Many attempts have been made to clarify this problem. We were fully aware of the opinion of Pryles (4) which clearly stated that a high colony count in clean-catch urine samples does not justify the diagnosis of infection of the urinary tract in patients with diarrhea, even if the count should exceed 100,000 colonies per ml. of urine, because the chances for a high degree of contamination are great; a careful catheterization is necessary to rule out contamination.

Catheterization is difficult to perform in infants under one year of age (more so in females), there is a high risk of contamination even under careful supervision (especially in females), and it is incovenient in outpatient clinics and in general practice. The

risk of introducing infection although low, is always present. The present study tried to determine whether we could avoid catheterization in these acutelly ill infants. Pryles (5) and others (6) have shown the validity of clean voided urinary specimens as compared to catheter samples in the diagnosis of urinary tract infection. Quantitative studies, that is, bacterial counts, correlate well with infection if over 100,000 colonies are present per cubic milliliter of urine.

Our results indicate that by adequate cleansing the incidence of pyuria sharply decreases. It also corroborates the finding of other investigations that below a year of age there is no sex difference as to this finding. The use of neomycin did not influence the presence of pyuria. There was no association between specific enteritis with Esch. coli and an increase incidence of urinary infection.

The study shows wide scattering and poor correlation between pyuria, colony counts and urine cultures. This method of collecting urine although an improvement over our usual routine is not the answer to establishing a diagnosis of urinary tract infection in infants with diarrhea. A study comparing clean catched urine samples collected in plastic bags versus catheterization is mandatory. Recent literature on this complicated subject offer new avenues for investigation (7, 8).

Summary

A study of samples of urine from 385 patients with acute diarrhea was conducted. All were infants below one year of age and 71% were below four months of age.

Clean voided urine samples collected in plastic bags were compared with those routinely obtained as to the incidence of pyuria. The incidence of pyuria was sharply reduced by this method of collection.

Bacterial colony counts were performed on all the clean voided samples (288) in order to establish a correlation between such counts and the diagnosis of urinary tract infection. No satisfactory correlation was obtained and the data points to a high degree of contamination by such method.

A study comparing clean voided samples of urine versus catherized samples is in progress in order to further investigate the most reliable method to be recommended in establishing the diagnosis of urinary tract infection in infants below one year of age suffering from acute diarrhea.

Acknowledgement

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Resumen

Se efectuó un estudio de muestras de orina tomadas de infantes menores de un año que se encontraban enfermos con diarreas agudas. El 71% de los infantes eran menores de 4 meses de edad.

Se comparó las muestras de orina eliminada, limpia, recogidas en bolsas plásticas con aquellas muestras recogidas en la forma acostumbrada, esto es, de micciones no limpias. Con el nuevo metodo se logró una disminuición marcada en la incidencia de piuria.

A todas las muestras de orina eliminada, limpia, (288) se le practicó un recuento de colonias para determinar el grado de bacteriuria. No se encontró una correlación satisfactoria que permitiese el diagnóstico de una infección del sistema urinario. Existe aún una marcada contaminación de la orina.

Otro estudio que compara las muestras de orina eliminada, limpia, con especímenes obtenidos por cateter se está efectuando para tratar de establecer el método más confiable que permite establecer el diagnóstico de infección del sistema urinario en infantes menores de un (1) año afectos por diarreas agudas

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ALCOHOLISM IN PUERTO RICO

F. J. Cabrera, M. D.
B. Bonet Fussá

Alcoholic beverages have been used as a supplement to the diet of man since the dawn of civilization. In many cultures wine and beer, like bread, have been considered as a symbol for survival. They have been widely used in religious rituals and other ceremonies prior to recorded history and its magic powers accepted as divine manifestations. The problems brought about by the use and abuse of these substances have been, in lesser or greater degree, universally concomitant with their availability. Alcohol was not invented but discovered by man more as a result of his curiosity than his ingenuity. Like fire and nuclear energy it should not be labelled as good or evil. It is the use that man makes of these substances what determines their positive or negative values.

Our assignment today is the discussion of the magnitude of the alcoholism problem in our island. In trying to fulfil this endeavor we would like to ask our audience to bear in mind that, aside from the syndrome known as alcoholism, alcohol poses a myriad of complex problems to our society which due to obvious limitations we cannot afford to explore in detail. Suffice it to say that whenever we refer to the social custom of drinking alcoholic beverages and alcoholism we are fully aware of the many factors, forces and issues that dynamically interplay in these processes.

The custom of drinking alcoholic beverages in Puerto Rico, like in many other countries, is closely woven into the fabric of our social interaction. We live, work and move in a society that is permissive to the use of alcohol; a society that condones alcoholic excesses in the group while condemning them in the individual. The great majority of our adult population (15 years and over) partakes of the social custom of drinking without apparent ill effects; for a minority (one out of every ten drinkers), the frequent and excessive use of this domesticated drug represents a tragic situation that often results in physical, mental, and social deterioration.

To define alcoholism is not a simple task. The Experts' Committee of the World Health Organization defined alcoholism in its relation to social factors. Based in this definition two well-known authorities in this field, Keller and Efron, defined alcoholism — "as a chronic illness, psychic, somatic, or psychosomatic, which manifests itself as a disorder of behavior. It is characterized by the repeated drinking of alcoholic beverages,

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to an extent that exceeds customary dietary use or compliance with the social customs of the community and that interferes with the drinker's health, or his social and economic functioning. Many special categories of alcoholics have been identified, including alcoholics who cannot control their drinking, and 'alcoholics with complications.' The latter are those whose excessive drinking has led to recognizable physical or mental sequelae." For the purpose of this paper we define as an alcoholic any individual whose drinking of alcohol repeatedly and seriously interferes with any or all the major areas of his life: his health, his social adjustment, his economic functioning or his interpersonal relationships.

Within the framework of these definitions can be situated the estimated 90,000 to 100, 000 alcoholics in our population. The great majority of those affected by this condition are still living in a family setting where the disruptive effects of this insidious and progressive illness are most devastatingly real. Cognizant that the alcoholic affects directly and adversely his immediate family nucleus (5.5 average persons per family in Puerto Rico) there would be around half a milion persons so affected — two thirds of them, children. It would never be possible to appraise, in terms of dollars and cents, the human costs, sufferings and deprivations of these families. This environmental substratum nurtures the seed-buds of physical, psychological, and social pathologies. Children that are brought up in this climate of distorted values and misdirected psychic energies would not have a fair chance to develop into healthy and emotionally mature individuals. Realizing the validity of these distress signals we come to agree with the so often quoted phrase — that alcoholism, if not biologically, is socially contagious.

The great bulk of our alcoholic population fall within the age range of 35-55 years. This is, potentially, the most productive period of their lives; when they have the responsibility of a home, children, and a job or business to attend. If the illness progresses undetected, or denied by the alcoholic and often by the family, in the absence of treatment, the end results usually are gloomy for the family members and disastrous to the alcoholic.

Alcoholism and alcohol related problems contribute a great burden to our industrial development and economy in general. The alcoholic employee is a great liability to his employer. In many ways he hampers production in industry, business, and public enterprises. Studies made in industrial areas comparable to ours' show that at least three per cent of the employees (workers and management) suffer from alcoholism. Their work records show an average absenteeism of twenty-two days per year attributable to this condition; tardiness, work accidents, and frequent familiar and financial entanglements.

Traffic accidents due to the mixing of alcohol and driving merit our most serious social concern. There is widespread agreement that drivers and pedestrians under the influence of alcohol are disproportionately represented in fatal accidents. A report from Connecticut for the year 1957 reveals that of all fatal traffic accidents, 35.1 per cent involved either a driver or pedestrian who had been drinking. In Puerto Rico, the Institute of Legal Medicine reports 115 necropsies due to traffic accidents for the year 1964 in the judicial districs of San Juan, Bayamón, and part of Caguas. Of these 115 fatalities 40 were pedestrians, 38 drivers, and 37 pas-

sengers; males 95, females 20, (17 male and female children under 14 years of age). Of the 40 pedestrians, 11 had been drinking prior to the accident, eight of them with blood alcohol levels above 0.15%; 23 of the 38 drivers had been drinking, 7 of them with blood alcohol levels above 0.15 per cent; 5 of the 37 passengers had been drinking, one of them with blood alcohol levels above 0.15%. Considering only the 98 adults involved in these fatalities, 39.7 per cent of them were under the influence of alcohol prior to the accident and 17.4 per cent were "legally intoxicated." It is interesting to note that 27.5 per cent of the pedestrians were drinking prior to the accident and 20 per cent were intoxicated; 60.5 per cent of the drivers had been drinking and 18 per cent were intoxicated.

There are many more problem-areas in our social environment in which the misuse and/or abuse of alcohol bear consideration as a significant contributing factor. We dare to affirm that whenever we find people in trouble we find problem drinkers or alcoholics.

Alcoholism presents a public health problem of major proportions in our environment. The great bulk of this serious socio-medical problem is still hidden in our community; hidden by the obscure clouds of prejudice, ignorance, misconceptions, deeply rooted cultural attitudes, denial, and avoidance. We agree with many other experienced workers in this field that to develop effective treatment and preventive programs it becomes necessary to treat the community so as to overcome these negative attitudes. In doing this it will be possible to mobilize and use the potential resources and skills of our fellow citizens to cope, in all its aspects, with this malady. Alcoholism and its sequelae of psychological disorders, social disruptions, emotional turmoils and physical infirmities characteristically strikes men and women during those years when they would otherwise be at the peak of their vocational productivity, when the fulfillment of their familiar needs is most needed, and when their potential contribution to the betterment of the society they live in is expected.

We must beware of treating and focussing on alcoholism as an isolated problem lest we lose our bearings toward the correct direction of shifting it over into the broader and general services of health experts and community and health resources if we want to achieve the long-range goals of the Alcoholism Control Program and Rehabilitation of the Alcoholic.

In our judgement we suggest that the following steps be taken in activating and mobilizing the community:

1. Accepting the disease concept of alcoholism makes the Department of Health of the Commonwealth of Puerto Rico responsible for the involvement and mobilization of all its professional and service facilities toward the treatment and prevention of this condition with the same vigor, willingness and disposition that is dealing with the other health problems that affect the health, productivity, and happiness of our fellow citizens.
2. To prevent distortions of the disease concept of the illness alcoholism the medical profession must accept the responsibility of their role in the treatment of alcoholic patients.
3. Other government agencies that in one way or other have to deal with alcoholism or its repercussions should foster and establish training programs for

the benefit of their personnel.

4. Formal study-programs should be integrated to the curriculae of the School of Medicine and Public Health.
5. The different colleges of the University of Puerto Rico should establish and integrate to their curriculae study units on alcohol problems and alcoholism (for teachers, social scientists, social workers, psychologists, lawyers, etc.).
6. The Intermediate and Secondary Schools should incorporate study units on alcohol problems and alcoholism in their curriculae.

In closing this short and incomplete discussion on the Magnitude of the Alcoholism Problem in Puerto Rico we deem it convinient to quote an excerpt from an article by an expert in this field, Marvin A. Block, B. S., M. D., "A Medical Blackout," published in Medical Tribune, December 7, 1962.

"A Medical Blackout"

"Is a physician well trained if he is unable to diagnose and adequately treat a disease that affects six to seven per cent of the total adult population? Is medical practice satisfactorily served when a disease ocurring in one of every 13 — 15 adults is neglected in both diagnosis and treatment by otherwise qualified physicians? Is a general hospital which denies admittance to patients with this prevalent disease a proper place for the training of interns and residents who later will care for the general public? Most physicians would shrink from the idea that this is possible. Yet alcoholism, a very insidious and progressive disease, is avoided by many physicians and its often reason for denial of admission to most hospitals. Far too often it is overlooked by practicing doctors who see these patients everyday.

Many interns and residents have never treated people suffering from alcoholism by the time they complete their training at their hospitals simply because the hospitals have denied admission to such patients. If these patients are sometimes admitted, it is often with a subterfuge diagnosis and the attention of interns and residents is thus misdirected so that the importance of the alcoholism is minimized.

Both the American Medical Association and the American Hospital Association have urged physicians and hospitals to treat these patients as they would other sick people. Unfortunately, the threat which this disease presents has not been met adequately. With no other illness would the medical profession be content to shift responsibility to lay people. Alcoholics need and deserve from their physicians the best medical attention. This responsibility presents a challenge which physician must meet."

EXPERIMENT IN THE TEACHING OF HUMAN BEHAVIOR

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J. E. Morales, M. D.

We could have entitled the paper The New Behavioral Science Program in the Department of Psychiatry, but that would have been misleading for a number of reasons. The recognition of the value of a liaison, between the Behavioral Sciences on the one hand and the medical profession including Psychiatry on the other has long been recognized. As early as 1910, Abraham Flexner pointed out the need for a broader education of the physician, to enable him to carry out his ever increasing functions in the social and preventive rather than solely in the individual and curative spheres. Behavioral scientists have frequently collaborated with physicians and psychiatrists to the benefit of all concerned, for example, Cora DuBois and Kardiner as well as numerous Culture and Personality studies carried out by Benedict, Mead, Metraux, Gorer and others.

What we are attempting here is also being tried in other departments in schools throughout the country, and the general trend is so clear that it would be presumptuous on our part to treat the idea as original to our staff and our Department.

But that the program is "new," is not a completely misleading statement either, since it is the first time that residents in Psychiatry in Puerto Rico have been freed to become full time students of Human Behavior, with all that that implies.

The primary aim of the program is for the residents to acquire on understanding of human behavior as it takes place anywhere, anytime in the community, before they learn how it manifests itself in the pathological distortions of reality which are encountered in the very special, and in a sense artificial community that we set up as wards or floors of psychiatric institutions. We feel that in this manner the residents will be better equipped to deal with abnormal behavior, while at the same time, able to start gaining knowledge of the forces that a community generates that directly influence the mental illness and/or health of its members.

It is our understanding that the proper study of man by physicians primarily concerned with the diagnosis, treatment and prevention of abnormal behavior, should begin with an appreciation of what so-called normal behavior is and what determines it.

The study of behavior has been largely neglected also in medical education. The natural sciences remain as the exclusive premedical requirement and the preclinical or basic sciences in the medical curriculum are still conceived by students and faculty as those deriving from Biology, Chemistry and

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Physics only. It is significant that the Department of Psychiatry started experimenting three years ago with a course in Human Behavior for first year medical students. This experience, probably more than anything else, fostered the innovative thinking and planning for the revision of the residency program.

Therefore we offer in the residency program a fundamental understanding of the basic concepts, techniques and methodologies of other behavioral sciences, principally anthropology, sociology and social psychology, so that they can be drawn on in a meaningful way by the psychiatrists, whether he be in a situation of private or government individual one to one therapy, group therapy, working with mental health programs at the community level, in intensive work in the hospital or whatever.

It is not our aim to try and make an "amateur" professional anthropologist, sociologist or social psychologist out of the resident, anymore than he would be expected to become a social worker, public health nurse, or a school teacher as a result of working with these professionals. But to be effective, he should have a better understanding of just when he can reasonable use these professionals to advantage in the treatment and prevention of mental illness, and how to go about securing their services. Perception and communication are crucial to this endeavor, and good training is one way to assure their acquisition.

But why are perception and communication of such prime importance? One's ability to perceive or even be aware of certain problems and possible solutions is based on one's understanding of the world around him, what one has been taught to perceive and what one becomes emotionally able to incorporate into his psychic apparatus. Certain alternatives do not even become feasible until they form part of the perceptual frame of reference of a person. With an understanding of the way in which sister disciplines look at and organizes concepts about human behavior, the language or technical jargon in which they do it, and the techniques and methods used, the psychiatrist is then in a position to decide when and how to make use of the knowledge accumulated in these other fields. Therefore, perception or awareness is crucial.

Communication is also crucial. A most decided effort has been made to get together the professional and the behavioral science staff with the residents also participating. Seminars, field experiences, discussion of pertinent literature is part of it but the most striking results have been obtained from the use of group dynamics techniques for sensitivity training. In July a three week laboratory (*laboratorio vivencial*) was held in which the teaching staff and the residents were participants. This has been continued in various ways, one of which is the Thursday afternoon seminar. Its primary objective is staff development. While the immediate goal is the preparation for the course in Human Behavior to first year medical students next semester, it goes without saying that everybody involved (about 36 people including first and second year residents) is experimenting with improved ways of communicating knowledge and feelings that increase our understanding of human behavior — not exluding one's own.

Without some kind of training effective communication is almost impossible. It is with this in mind that our training was elaborated. Some things are tried and true

pedagogical devices, with tried and true professional content. Other aspects of the program are somewhat more experimental.

All of this, of course, is aimed at turning out first rate psychiatrists in the traditional sense of the profession of psychiatry. The hope is that it will be done in such a way as to improve the field of psychiatry by increasing its ability to deal with both mental health and mental illness, and, at the same time, facilitate the use of psychiatry and psychiatric principles by other behavioral scientists and other professional interested in the welfare of the individual and the community. Such a psychiatrist will indeed be treating the whole man, by treating him in his entirety which would include his environment — his family (which has long been recognized as of prime importance), his community, its structure and function, and his culture with all its norms, values, integrating and desintegrating forces.

Ultimately it might be possible that the preventive goal could become as stimulating a prospect as the therapeutic one for the psychiatrists of the future. Their simultaneous development during the training period heightens awareness of emotional processes in human transactions, and creates the environment for a synergistic effect.

It is for these reasons that we feel that the time has come for the formal and informal integration of the behavioral sciences into the medical curriculum in general and the psychiatric curriculum in particular. At the attained level of living in Puerto Rico and the United States, health is no longer solely a matter of "not dying" — today we can and should be concerned with living, with health in the broadest sense of that term, and with prevention.

A melding, or merger if you like, between these two areas of endeavor is essential since one is incomplete without the other. The study of man makes sense in the context of health (medicine, psychiatry). Health in turn is less meaningful without the sciences of human behavior.

Our experiences to date have been multiple and varied. The teaching method has been both formal and informal in nature. Prepared lectures on the nature and scope of anthropology, the concept of culture, systems of classification as heuristic devices, patterns of courtship and marriage in the Puerto Rican family, concepts of marriage and kinship applicable to any society have formed some of the content of the more formal material. The residents have also read and prepared reports on different ethnic groups for presentation to the rest of the group.

Many discussions have been conducted on the role of the behavioral sciences in a residency program in Psychiatry, the relationship between doctor and patient — the role of family and community in the formation of norms and attitudes, the effects of status and role on human behavior and interpersonal relationships, the relationship between science and magic, the residents, own attitudes toward man and society and the extent to which these attitudes influence perception and communication.

Numerous examples of impromptu experiences are used to demonstrate the concepts of family and community as well as other areas of social structure and function such as political organization, economic organization, ecology, religion, art and leisure.

Field trips have been made in which the residents have been able to see themselves in action and later examine the efficacy of their

approach.

Peer teaching is the norm for the behavioral science material with the teacher utilizing the Socratic method of teaching. Numerous readings have been assigned — and their interpretations are elicited from the residents themselves with the guidance of the instructor.

A number of social scientists and researchers have contributed generously of their time in this collaborative effort, and still more have indicated their willigness to participate. Guests lectures have been given covering small group structure sociologically defined, deviance, socialization learning theory, including operant conditioning, interviewing techniques, and social research in Puerto Rico.

Teaching is to the whole individual — so that the timing of the introduction of certain materials and the intensity of the experience itself have been planned in terms of the emotional as well as intellectual receptivity of both teacher and student, as opposed to a rigidly predetermined plan of action.

The members of the Mental Health Staff, and those from the Department itself have made efforts to coordinate, and integrate into the new program. One of the greatest indications of cooperation is the enthusiastic and active involvement in the Thursday afternoon Seminar for the Staff on Human Behavior.

The first year residents, who in many senses are the stars of this performance, have cooperated energetically and truly given of themselves in this ventures. They have been faced by the many pressures that being in the ambivalent position of being "first" can frequently bring about. They are to be commended for their willingness to work and grow.

In summary and conclusion, the staff realized that it is the unusual ex-resident who, after the traditional clinical training in psychiatry, becomes interested enough to learn about the community from which his patients come. This neglect or apathy applies both to the community as such, and to the theoretical constructs that he could derive from the behavioral sciences which would serve to explain in a more understandable way the forces of group, society and culture, and in such a way as to make them more researchable. Once the former resident busies himself in clinical practice at hospital, clinic or private office, it becomes increasingly difficult to truly visualize other approaches to behavior than the psychodynamic one that he has learned so well.

Thus, it made sense to us to initiate the residents in the fashion previously described. It is quite possible that this first effort falls short of our mark on several counts. Its evaluation cannot be made merely on what the residents achieve this first semester, however excited we may be with their accomplishments. One must await the more convincing proof as to whether this knowledge and experience-based learning makes for better psychiatry in the future. What will be our measuring stick to determine that? There are no controls except for past experience with another style of training. Surely something should be discernible in the future therapeutic work of these trainees with their patients, regardless of the type of practice that they choose. What we are sure will be rather difficult to adjudicate is the worth of the preventive work of these trainees.

A whole new field is opening in Psychiatry: assessing the nature of mental health and the prevention of illness. Work with

children has gained paramount importance as witnessed by the increasing involvement of mental health professionals in schools, Operation Headstart, and the like. From our own program all the third year residents chose to take the two year fellowship in Child Psychiatry.

Efforts have been made by Sibylle Escalona and others to predict the outcome of normal infants as far as personality is concerned. Longitudinal life-long research of patients seen during their childhood are now in progress at various places (Stella Chess in NYC for example), and should become routine procedure here. It is true that from the preventive point of view human behavior presents problems much more difficult to surmount than is the case with communicable diseases such as malaria or polio, but the challenge is here. The more we pull together, and meld, the more we will be able to meet it.

PROTEOLYTIC ENZYMES
Fundamental Concepts on Their Chemistry, Uses and Biological Importance

E. Toro Goyco, Ph. D.

The term *enzyme* has become very familiar to all of us involved in any aspect of the broad field of biology. An enzyme may be defined as a complex catalyst of biological origin which has a high degree of specificity and a very marked efficiency. Because of this, enzymes which are present in all living organisms catalyze metabolic reactions rapidly through well-defined pathways.

Historical

Reactions catalyzed by enzymes have been profitably used by man long before the advent of written history. According to Greek mythology, Bacchus discovered fermentation to produce wines. Nowadays it is a well established fact that fermentation is a result of the anaerobic carborydrate metabolism performed by a series of enzymes. In fact, enzymes have been alternatively called ferments. In addition, such industrial processes as the making of cheese, the leavening of bread, the manufacture of vinegar, are enzymatic processes that stem from antiquity.

The work of Louis Pasteur laid the foundations for the study of enzyme-catalyzed reactions in living cells. However, he concluded that these enzymatic processes occurred only in intact cells. The discovery of the Buchner brothers that the cell free preparations were capable of causing fermentation gave a great impetus to enzymology. The subsequent studies in enzymology, with the further isolation of enzymes, their purification and crystallization, studies on their chemical composition and mechanism of action have been some of the most extraordinary chapters in scientific achievements accomplished by man in any period of its history. Such magnificent accomplishments have been performed in a relatively short period of time since James Sumner in 1926 crystallized the first enzyme and determined its protein nature.

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On Enzymes in General: Nomenclature and Classification

It has already been stated that enzymes are very specific chemical entities, thus catalyzing mostly an individual chemical reaction As a rule, enzymes are named in terms of the reactions they catalyze. The customary practice is to add the suffix-ase to the name of the substrate where by substrate it is meant the substance upon which an enzyme acts. Thus the enzyme attacking urea to produce CO_2 and NH_3 is named urease. The enzyme present in the liver and responsible for the production of urea by its attack on arginine has been named arginase. Nevertheless, some

of the older nomenclature has persisted and still the names pepsin, trypsin, rennin, etc., are in common usage. It is not unusual to name the proteins after the source from which they are obtained. We thus may become familiar with such names as papain, ficin, bromelin, pinguinain, etc.* Enzymes are also classified in groups according to the groups of substances of biological importance that are subject to their action. We thus have carbohydrases, lipases, proteinases, to cite a few. As is obvious, carbohydrases will exert their enzymatic effect on carbohydrates, lipases on lipids and proteinases on proteins. This review, which by no means pretends to be exhaustive is concerned esentially with the group called proteases, proteinases or proteolytic enzymes.

On the Susceptibility of Proteins to Enzymes

The recognition of the physiological importance of the proteolytic enzymes derived in first instance from the role they play in the degradation of the dietary proteins. Although first they showed predominantly in the gastrointestinal tract, it is now known that they are generally distributed. The liver, kidney, brain, endocrine glands and other tissues are rich sources of proteolytic enzymes. Plant tissues as well as microorganisms are also rich sources of proteolytic enzymes, as will be later shown.

The physiological importance of these enzymes will not be stressed for the time being, but it will be noted that their study is inextricably linked not only to gastrointestinal digestion and disorders of this tract, but also to such problems as mechanism of blood coagulation and dissolution of blood clots, milk clotting, release of hyper and hypotensive agents, inflammation and anti-inflammatory agents, autolysis, and many other physiological processes. Prior to a more detailed mention of some of these phenomena, it would be advisable to enter briefly into their mode of action.

The Peptide Bond and Hydrolysis

The discovery that there were peptide-bond-cleaving enzymes was due to the observation of the action of proteases on proteins. No clear understanding of the reactions was available until Emil Fischer demonstrated that proteins are made of peptide bonds. A digression is in order to explain the origin and meaning of the peptide bonds.

It must be indicated that the building blocks of those complex units named the proteins are smaller units called amino acids. These units, containing at least one amino and one carboxyl group, are joined together by nature in a very ingenious fashion, thus creating an amino acid chain that will eventually give rise to 'the protein molecule. Various forces or bonds may get to act together, thus giving a protein molecule its particular composition and configuration. By far the most important entity contributing to create that structure is the peptide bond, which is a product of the chemical combination of the carboxyl group of an amino acid with the amino group of another amino acid molecule (Fig. 1). How this combination occurs in vivo is beyond the scope of this review. The bond so formed is called

Papain is the name given to enzymes present in the latex and fruit of Carica papaya; *ficin is a mixture of proteases found in the sap of some* Ficus *species; bromelin is the name given to a mixture of enzymes present in the fruits, leaves and stem of the pineapple plant; Ananas sativus and pinguinain is found in the fruits of the maya plant* Bromelia pinguin L.

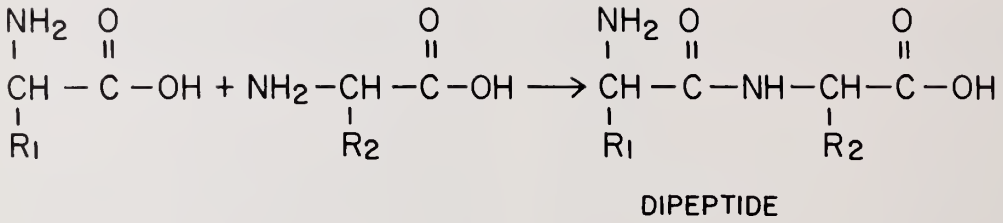


Fig. 1: The amino group of amino acid (R_1) combines with the carboxyl group of amino acid (R_2) forming a dipeptide. The new dipeptide has in turn a free carboxyl and a free amino group. These in turn are capable of forming peptide bonds thus elongating the amino acid chain.

a peptide. Its formation is accompanied by the liberation of water and the consumption of a small amount of chemical energy. The new chemical entity being formed, besides containing a peptide bond will have, in addition, one free carboxyl and a free amino group. The free amino in turn will be able to combine with the carboxyl of another amino acid, thus creating another peptide bond and a longer chain. This process leads to the formation of the protein molecule through the production of these chains, which comprise the background of the protein molecule. Each protein may contain one or more of these chains. The action of proteolytic enzymes is precisely at the so-called peptides. The suffix "lytic" in proteolytic means having the capacity to introduce the elements of water, thus regenerating the amino and the carboxyl groups.

Exo and Endo Peptidases

The proteolytic enzymes may show preference for peptide bonds located in the middle of the chain of amino acids, or may show preference for the splitting of the peptides at the ends of the chains. The names endopeptidases for the former group and exopeptidases for the latter has been coined by Bergmann (1). Among the most commonly known endopeptidases are pepsin, trypsin and chymotrypsin from animal origin and papain, bromelin, ficin and pinguinain from plant origin. The fact that they are endopeptidases does not imply that they will cause the splitting of a protein at the same site. Each one has a preferent bond where it will act.

Since a protein molecule has two ends, a basic (amino group) and an acid one, we may expect the exopeptidases to be of two sorts. One of the groups is called the carboxypeptidases, showing preference for peptides near the free carboxyl group, and the amino-paptidases, which show preference for the peptide ends containing the free amino group.

Chemical Nature of the Peptide Bond Cleaving Enzymes

Enzymes themselves are proteins, thus they are very complex and their molecular

TABLE I: MOLECULAR WEIGHTS OF SOME COMMON PROTEOLYTIC ENZYMES

Enzyme	Molecular Weight (a)	Source
Pepsin	35,000	Gastric mucosa; chief cells
Trypsin	23,000	Acinar cells of pancreas
Chymotrypsin	26,000	Acinar cells of pancreas
Thrombin	15,000 (b)	Liver synthesized prothrombin
Carboxypeptidase	34,000	Acinar cells of pancreas
Leucine amino peptidase	300,00	Intestinal mucosa
Subtilisin	25-30,000	B. subtilis
Plasmin	108-127,000	Blood pasminogen
Papain	21,000	Carica papaya
Bromelin	36,000	Ananas sativus
Pinguinain	19,000	Bromelia pinguin
Ficin	26,000	Several Ficus species

(a) Average molecular weights. Different physical methods used may yield different results.
(b) Minimum molecular weight.

weights may be very high (Table I). That complex structure, however, takes care of just a tiny fraction of the substrate, in some cases a single peptide bond. Studies have shown that the enzyme has a small portion of its structure which performs the job of hydrolyzing the peptide bond. This small portion of the enzyme structure is named the *active site.*

The active site is the locus at which substrate binding to the enzyme occurs and which also participates in the catalytic reaction mechanism. These loci are formed by amino acid residues. Some of the chemical groups making these loci have been already identified in several enzymes by the use of ingenious chemical techniques. The theory has been postulated that at least three points of attachment of the substrate at the active site are needed for the catalytic effect to occur (2).

Chemical Groups Essential for Enzyme Activity

Some chemical groups are known to be of paramount importance in determining the hydrolytic activity of enzymes. Among these, we may consider the following:

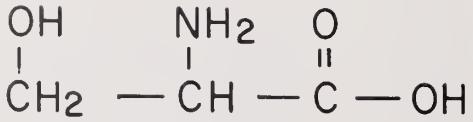
a) *thiols or sulfhydril groups:*

These are present as part of the amino acid cysteine. The plant proteolytic enzymes, in general, depend on the presence of these for enzymatic activity. This is also true of some bacterial and fungal proteinases (3). A group of intracellular proteinases found in animals named the cathepsins are also known to depend on sulfhydril groups for enzymatic activity (4, 5). These enzymes can be rendered inactive by any chemical agent combining in one way or the other with the sulfhydril group.

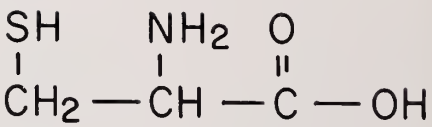
b) *hydroxyl groups:*

Many proteolytic enzymes of animal origin depend on the presence of these chemical groups in their structure for their enzymatic activity. The hydroxyl group is present in the amino acids serine and threonine (Fig. 2).

Among the enzymes showing the essentiality of this group are trypsin, chymotrypsin,



SERINE



CYSTEINE

Fig. 2: The amino acids serine and cysteine differ in only one atom. Both the SH and OH groups are essential for enzymatic activity. Plant proteolytic enzymes, and some bacterial and fungal proteinases depend on the presence of SH groups for enzymatic activity, while the proteolytic enzymes of the gastrointestinal tract depend on hydroxyl groups.

and thrombin (6). Some non-proteases are also known to show this essential group, among which cholinesterase is found (6). These enzymes lose their activity upon exposure to organophosphorus compounds like di-isopropyl fluophosphate (DFP) and its derivatives (7, 8).

In addition, some proteolytic enzymes may need bound metal ions like Mg, Mn, Co, Zn, and Fe to show enzymatic activity. The metal may be either loosely or strongly bound. The most accepted hypothesis is that the charge of the metal ion supplies the third point of attachment necessary to hold the substrate for the enzyme to act. Any agent that may preferentially hold the metal, like a chelating agent as versene (ethylene diamine tetra-acetate), is capable of lowering or even fully abolishing the activity of the enzyme. The opposite of this activating effect of metals may occur in some enzymes, namely in those depending on free sulfhydril groups for enzymatic activity. The presence of heavy metals leads to a complex formation, forming sulfur-metal bonds which render the enzyme inactive. In those cases a chelator plus a reducing agent are very efficient in restoring proteolytic activity.

Factors Affecting the Activity of Proteolytic Enzymes

Several factors are known to exert a more or less pronounced effect over the activity of enzymes. Although not exhaustive, the following is a list of the factors which determine to a large extent the activity of proteolytic enzimes.

a) *hydrogen ion concentration (pH)*:

This factor shows spectacular effects on proteolytic activity. Proteolytic enzymes, as enzymes in general, are extremely sensitive to variations in hydrogen ion concentration. There is a range in the pH spectrum where proteolytic activity is more pronounced. At either side of this pH, the activity is greatly diminished. The hydrogen ion concentration where maximum activity occurs is termed the pH optimum. This may be either on the acid or alkaline side. A striking illustration of how pH optimum may vary in different enzymes is shown by the proteases of the gastrointestinal tract. While pepsin has a pH

optimum on the acid side (9, 10), trypsin and chymotrypsin show theirs on the slightly alkaline side (10, 11). Placing pepsin in a less acid medium will cause its inactivation. The pH at which pepsin shows maximal activity would cause the denaturation of most proteins. Pepsin is, under these conditions, very stable. There may reside, teologically, the explanation for its presence in the very acid juices of the stomach. The increase of the pH of its ideal medium, as in achloridia, will bring forth a marked diminution of its enzymatic activity. The behavior of trypsin and chymotrypsin is similar to that of pepsin. The removal from their optimum environmental conditions (the weakly alkaline pH of intestinal juice) will render them inactive.

Other proteolytic enzymes may show different pH optima. Our experience with the enzyme pinguinain shows its optimum pH to be slightly acid (ca 3.8). This, incidentally,

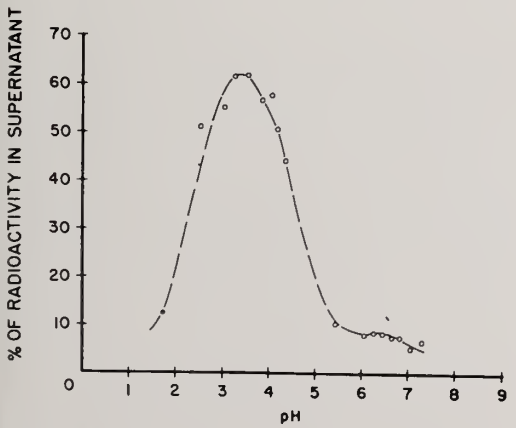


Fig. 3: The most pronounced proteolytic activity occurs at a pH of 3.8 when using human serum albumin as substrate. The percent radioactivity in supernatant is an index of the ability of the enzyme to change the intact albumin molecule to smaller pieces not precipitable by trichloroacetic acid.

is the pH of the juice where it is found. As can be easily appreciated from Figure 3, a change in pH toward either side markedly reduces the activity of the enzyme. The enzyme papain has an optimum around 6 (12) and so does bromelin (13). Maximum advantage of the tissue digestive capacity of these enzymes is taken when incubation is performed at pH close to the optimum. This implies that for more efficient uses of these enzymes in vivo, those having optimum pH near physiological are preferable. This, although by no means the only parameter to be considered when using proteolytic enzymes for therapeutic purposes, is a factor to keep in consideration.

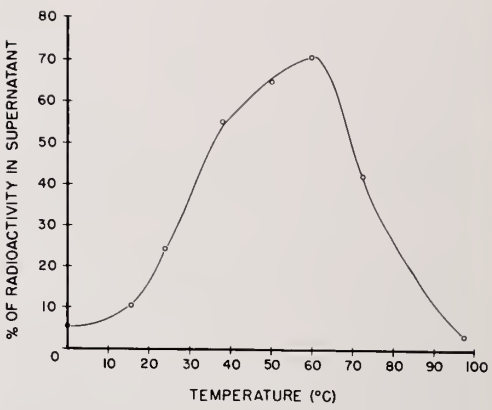
Alterations in proteolytic activity with changes in pH may sound extraordinary to somebody not quite familiar with the fields of enzymology and protein chemistry. Actually, protein chemistry supplies a straightforward explanation for these changes. Enzymes, being proteins, have a very characteristic chemical architecture where a definite orientation and location of chemical groups takes place. The hydrogen ion concentration may exert a profound influence on the configuration of the protein molecule. Innumerable studies have shown that the shapes of these molecules change as the pH is varied. These changes are caused by the appearance and disappearance of charged groups within the molecule. This may lead to the attraction and repulsion of existing chemical groups within the same molecule. The charged groups that make the active site of the enzyme may be caused to disappear because of a shift in pH. A new electrical charge may appear in the neighborhood of the active site, thus causing either attraction or repulsion, consequently altering the spatial arrangement of the charged groups that

make the active site, hence disrupting the natural architecture. This disruption may be transitory in nature or it may be permanent. This disruption of the chemical architecture is termed denaturation, and in the case of enzymes causes the permanent loss of enzymatic activity.

b) *temperature*:

Being a catalytic process, enzymatic action is highly dependent on temperature. Low temperatures lead to a diminution in enzymatic activity, with a virtual stop while a rise leads to an acceleration of the reaction. The increase in activity with temperature is exponential. There is a limit, however, in the temperature at which enzymatic reactions can take place, because otherwise a loss in enzymatic activity might ensue. This is due to the fact that excess heat causes a disruption in the chemical architecture of proteins. Between the limits of temperature lies a most convenient point named the optimum temperature at which the activity of the enzyme is more pronounced. Most enzymes, including proteases, are relatively inactive at temperatures close to freezing while temperatures in the neighborhood of 60°C inactivate them by denaturation. Therein lies the rationale for preservation of foods by freezing or boiling. Some enzymes show a marked resistance to heat, preserving their activity at temperatures that render most proteins inactive. Significant among these are the proteolytic enzymes papain, from the papaya fruit and pinguinain, from the maya fruit. The variation in proteolytic activity with temperature for pinguinain are shown in Figure 4. The optimum temperature of 65°C is unusual, making it a very suitable enzyme for industrial purposes, such as that of meat tenderizing.

c) *inhibitors*:



The concept of enzymatic action already presented is that the enzyme combines with the substrate, forming a complex. This may be illustrated simply as E + S = ES. The complex rapidly dissociates to yield the enzyme in its free form again plus a product of the reaction (14). Thus the whole process can be expressed as follows:

$$E + S = ES — E + P.$$

It has been already stated that in the case of proteolytic enzymes, there is a portion of the substrate which is selectively attacked (peptide bond). There is a definite locus in the enzyme (the active site) which exerts the attraction of the peptide bond and where the rearrangement of the atoms and liberation of energy leading to the hydrolysis of the bond occurs. Some chemical agents (not substrates) may be easily attracted to the active site of the enzyme, thus making it unavailable to the substrate. The consequence of this effect is a reduction of enzymatic activity. Agents capable of doing this are termined inhibitors. Proteolytic enzymes depending on sulfhydril groups for enzymatic activity, that is, having a sulfhydril group at the active site, are easily inactivated by agents

TABLE II: ACTIVATION OF CRYSTALLIZED PINGUINAIN*

Sample No.	Activator	% 1-131 Albumin Converted To T.C.A. Soluble Radiocativity
1.	None	1.0
2.	1.0 ml 0.05 M thioglycollate	43.3
3.	2.0 ml 0.05 M thioglycollate	38.9
4.	1.0 ml 0.05 M L-cysteine.HCl	28.7
5.	2.0 ml 0.05 M L-cysteine.HCl	34.9
6.	1.0 ml 0.05 M NaCN	0.9
7.	2.0 ml 0.05 M NaCN	0.9
8.	1.0 ml 0.05 M ascorbate	0.6
9.	1.0 ml 0.1 M ascorbate	0.6

**Incubation performed in 0.1 M acetate buffer, pH 4.0 at 37°C for 20 minutes. Incubating mixture contained 3.0 mg crystallized pinguinain: 80 mg human serum albumin with 0.4 uc 1-131 labelled albumin as tracer; activators as indicated and a total volume of 10 ml.*

reacting with this group. Hence heavy metals such as mercury, mercury compounds, oxidizing agents as iodine, or even exposure to the air, may cause the inactivation of sulfhydril containing enzymes. The poisonous effects of mercurials, iodinated compounds, and other oxidizing agents are essentially due to the oxidation of sulfhydril groups. This inhibition or poisoning can be counteracted by reducing agents, that is, compounds that restore the sulfhydril group to its native state. Table II shows the effect of reducing agents on pinguinain, a sulfhydril dependent enzyme.

An analogous situation occurs with the hydroxyl groups present at the active site of other enzymes. Other chemical agents combine specifically with these groups, thus rendering the enzyme inactive. This is the mechanism by which organic phosphorus compounds like malathion and parathion inhibit enzymes, including the proteases trypsin, pepsin and chymotrypsin (7, 8).

The reaction between the chemical inhibitor and the chemical group at the active site may be reversible. In this case addition of excess substrate may compete for the site with the inhibitor. From purely probabilistic considerations, it follows that the higher the concentration of substrate, the higher the opportunities of cancelling out the inhibitory effect. This type of inhibition or enzyme poisoning is termed *competitive inhibition.* When the inhibitor combines irreversibly with the enzyme, there is no chance that the substrate will replace the inhibitor once it has combined with the chemical group at the active site. Enzymatic activity will remain diminished no matter how much substrate is added to the enzyme. This kind of inhibition or poisoning is termed *non-competitive inhibition.* This irreversible combination of the inhibitor with the enzyme may occur (a) at the active site of the enzyme, thus making the site unavailable to the substrate, or (b) at some other place in the structure of the enzyme molecule, thus disrupting the arrangement at the active site and a loss of enzymatic activity.

Methods of Enzymatic Assay

Enzymatic activity is a fundamental concept in the study and understanding of the kinetics of proteolytic enzymes. It means the rate at which the enzymes successfully attack the substrate. The turnover number, a parameter used to measure enzymatic activity, is defined as the number of moles of substrate acted upon per mole of enzyme per unit time (usually a minute). A high turnover number indicates a rapid rate of enzymatic activity, while a small turnover number implies the opposite. It is not always feasible

to perform this type of exact quantitative measurement and therefore a wide variety of conventional methods have been developed for the assay of proteolytic activity. These may vary from very rudimentary measurements to very sophisticated laboratory techniques. Some of these methods, the measurements made and the principle behind them, are listed in Table III.

A very simple method for the detection of proteolytic activity listed in Table III is the determination of the milk clotting activity. It has a serious disadvantage, however, because not all proteolytic enzymes are capable of causing the clotting of milk. Another simple method for the determination of enzymatic activity is the measurement of the soluble nitrogenous compounds produced after incubation of the enzyme with a protein substrate. In this assay, the incubation mixture is precipitated by trichloroacetic acid, a selective protein precipitant. The unhydrolyzed protein, as well as the enzyme, are precipitated, but the products of enzymatic hydrolysis are not subject to precipitation, thus remaining in solution. These non-precipitable substances are then measured by either of several methods. As the time of exposure to enzymatic action is increased, the amount of non-precipitable products is increased. By the same token, the higher the amount of enzyme present in a given mixture, the higher the amount of non-precipitable nitrogenous compounds.

TABLE III :SOME METHODS FOR THE ENZYMATIC ASSAY OF PROTEASES.

Method	Measurement Performed
Milk clotting	Time (secs) taken for clot to appear (1).
Gelating liquifying	Decrease in specific viscosity of gelatin solution (2).
Casein or hemoglobin digestion	"Tyrosine" in T.C.A. (a) soluble supernatant after enzymatic hydrolysis (3, 4).
Azocol digestion	Increase in color followed spectrophotometrically (5).
Esterase activity	Hydrolysis of esters followed spectrophotometrically (6).
Amidase activity	Ammonia produced (7).
Radioiodinated serum albumin digestion	Radioactivity in supernatant after precipitation by T.C.A.
Clotting time	Time taken to shorten clotting time of fibrinogen solution at pH 7.2 (8).

(a) *T.C.A. = trichloroacetic acid.*

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Following this same principle, a simple method has been worked out and followed in our laboratory. The substrate used has been radioactive human serum albumin labelled with I^{131}. Addition of trichloroacetic acid to the protein will cause the precipitation of all the radioactivity. After exposure to proteolytic enzymes, a number of the albumin molecules is hydrolyzed to small units not subject to precipitation with trichloroacetic acid. The higher the enzymatic activity, the more marked will the amount of radioactivity left in the supernatant be after a given incubation period.

The most recent and elaborate laboratory techniques have had as objective a more thorough quantitation of enzymatic activity. Since proteolytic enzymes are specific for certain peptide bonds, synthetic peptides are made and these, rather than the whole protein molecules, serve as substrates. A wide diversity of synthetic peptides are now in use and the laboratory methods for detecting their sensitivity to enzymes have become more precise. Using these elaborate techniques, quantitative estimation of proteolytic activity in enzymes from digestive juices has been very well achieved.

Practical Uses of Proteolytic Enzymes

a) *Industrial and Commercial:*

Several million pounds of proteolytic enzymes are produced and sold in the world market every year. Over half million pounds of crude papain alone were sold in the U.S. in 1957 (12). The textile industry consumes large amounts of proteolytic enzymes every year. These are mostly used for the prevention of wool shrinkage. Proteases are also widely used in the beer industry to prevent oxidation and the chill hazes in the beer. Proteases are also used in the tanning industry to bate skins and hides. These enzymes are also used in the manufacture of chewing gum. The most important constituent of the commercial meat tenderizers is always a proteolytic enzyme. A generalized practice now in use in the slaughter houses in the United States is the intravenous injection of proteolytic enzymes to cattle few minutes before sacrifice. This method of meat tenderizing has the advantage of allowing the enzyme to act in the tissues since a few minutes prior to death of the animal, thus allowing a better distribution and a more efficient action.

b) *Laboratory uses:*

Proteases are widely used in the laboratory in problems dealing with protein chemistry. In the performance of hemagglutination tests, erythrocytes are washed and treated with substances which favor the adsorption of antigens. A procedure has been devised by which the erythrocytes are washed with solutions of proteolytic enzymes. In doing so, enzymes wipe out by hydrolysis the interfering proteins adhered to the red cell stroma, thus allowing a better adsorption of antigenic material upon exposure of the erythrocytes to antigen. This facilitates the hemagglutination phenomenon upon addition of the specific antibody against the adsorbed antigen (15, 16).

Fundamental studies on the structure of the immunoglobulins have also been performed taking advantage of the fragmentation of immunoglobulins by proteolytic enzymes, especially papain (17, 18).

Tissue digestion can be accomplished under milder conditions when done by proteolytic enzymes. In our studies with the protease pinguinain at the San Juan Veterans Administration Hospital, a method has been developed for the isolation of *S. mansoni* ova

from the tissues of infected mice (19). This technique promises to be a significant step forward in the possible use of the circumoval test for schistosomiasis (20) in routine laboratories in many places in the world.

c) *Therapeutic Uses:*

A wide variety of therapeutic uses have been given to proteolytic enzymes. It is not our intention to evaluate their usefulness since claims and counter claims of their efficiency are abundant in medical literature. For an excellent discussion, see Innerfield (21).

The oral use of proteolytic enzymes for therapeutic purposes is highly questionable from the scientific point of view. The highly acid pH of the stomach alters markedly the properties of proteins. Proteolytic enzymes, being proteins, are either denatured or digested. Pepsin is one of the few exceptions to the rule and that is possibly why in the evolutionary process it has evolved to exert its activity there. The therapeutic use of pancreatic enzymes to supplement a deficiency in the enzyme production of the pancreas is, in our opinion, of very limited usefulness.

The use of proteolytic enzymes in the treatment of inflammation is becoming more frequent. There is scientific basis for such an approach. Inflammation is characterized by autocatalytic cell destruction. In progressive inflammation, a decreased rate of proteolysis and the presence of high molecular weight proteins is observed. The added proteases enhance proteolysis, making diffusion of products through tissue membranes considerably easier, thus decreasing osmotic differences which are the physical basis of inflammation. In addition, the claim is made that some polypeptides are "vectors" of inflammation (21). Proteolysis by proteases remove these vectors.

The techniques of enzymatic zonulolysis for intracapsular extraction (22) has been developed and used in the last decade. This technique rests on a valid scientific basis from the point of view of protein chemistry. Delayed wound healing, a complication that may arise after using this technique, has been attributed to the effects of enzyme that has remained "in situ" after surgery (23). The pros and cons of this technique have been discussed by Castrén (24).

The possibilities of using proteolytic enzymes in pediatrics are very promising for the treatment of hyaline membrane disease (25), since this is a condition caused by the inability to hydrolyze fibrinogen. This is an interesting area in which much fundamental research needs to be done.

On the basis of early experiences with a limited number of patients, Smith (26) has claimed that chymopapain, injected into an intervertebral disc, relieves the signs and symptoms caused by herniation of nucleus pulposus from that intervertebral disc. Results like these, so subjective in nature, need further confirmation.

Many reports in medical literature call attention to the harmful effects of enzyme therapy. Using rabbits as experimental animals, Kelner and Robertson (27) were able to induce necroses of cardiac and skeletal muscle after intravenous injection of proteolytic enzymes. None of the enzymes used, however, (papain, ficin, trypsin and streptokinase) were pure. A similar finding was reported by Ruffolo (28) using papain, but once again his enzyme was not pure. Hulth and Westerborn (29) reported the experimental production of dwarfs in rabbits treated with papain but their work dealt with ani-

mals treated with massive doses of impure papain from shortly after birth.

It can be concluded that the use of proteases, as of any chemical agent, has its limitations. Many of the therapeutic values claimed by some investigators have not been confirmed by others. Besides, there are some factors that we must per force accept in their proper perspective. There is quite a difference between what is scientifically established and what is claimed from misinterpretation of results obtained in a single research work. Besides, commercial propaganda sometimes unfortunately permeates scientific journals in the form of papers.

Biological Significance of Proteolytic Enzymes

It would be hopeless at this state of our knowledge to attempt an evaluation of the significance or value of proteolytic enzymes in living cells. We certainly know part of their usefulness in the gastrointestinal tract, but aside of that, not much is known. We are totally ignorant, for example, on what is the physiological function of papain in the papaya fruit, or blomelin in the pineapple, or pinguinain in the maya. They, nevertheless, may be performing one or several physiological functions.

The presence of a group of intracellular proteolytic enzymes in animal tissues whose physiological role has not been clearly elucidated, deserves a special comment. The group of proteolytic enzymes named the cathepsins is found in so many organs that they may be considered an obiquitous component of animal tissues. Among mammalian organs, kidney, spleen, liver and lung are among the richest sources. A variety of cathepsins have been identified but three of them conventionally denominated A, B, C, have been more thoroughly studied. They are characterized by having a pH optimum on the acid side and being dependent on the presence of sulfhydril groups for enzymatic activity (30). Although their action is evident during autolysis of animal tissues, a process which is favored by an acid pH, it is not known, as stated previously, what role, if any, they play in the living cell. The fact that these enzymes exist in the living cells without causing any disruption in the cell structure that is essentially a protein matrix, lead Gianetto and de Duve (31) to postulate a very interesting hypothesis. There is in the living cell a special organelle, which they named the lysosome, which represents a repository of autolytic enzymes such as the cathepsins, ribonuclease, deoxyribonuclease, acid phosphatase, etc. The hypothesis implied the possibility that these enzymes are non-functional in the living cell but exert their effect upon release from the lysosome, after death of the cells. Considerable work on histochemistry and electron microscopy confirmed the correctness of the hypothesis, thus being the first time that a biochemical hypothesis served as the basis for the identification of an up to then unknown anatomical entity. We may speculate on the physiological function of these intracellular proteolytic enzymes as follows: After cell death, they cleave the intact proteins of the dead cell, and even the dead cell protein matrix, thus changing these fragments so that they can be used for protein formation by neighboring living cells.

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EDITORIAL

¿HACIA UNA MEDICINA MAS CIENTIFICA?

Se opina en ciertos círculos, generalmente de legos en la materia, que la medicina de un país de recursos limitados como el nuestro debiera ser eminentemente práctica. Se piensa que hasta el momento la medicina puertorriqueña, especialmente en su estructura asistencial, ha avanzado considerablemente sin necesidad de grandes recursos en la enseñanza, o en la investigación médica. La escasez de médicos prácticos se atribuye a que nuestras instituciones de enseñanza de la medicina han desvirtuado su propósito de crear médicos eminentemente prácticos, formados para afrontar y resolver los problemas inmediatos de la salud pública. Tales opiniones surgen de la ignorancia de lo que es, o debiera ser, un médico práctico. La medicina, como ciencia aplicada, es de necesidad eminentemente teórica y práctica en proporciones idénticas. La restricción en lo teórico transciende de inmediato a lo práctico, su negación conduce inexorablemente al empirismo. Quizá el punto vital del intrincado problema médico-asistencial de nuestro país no es tanto la escasez en la medicina práctica como el exceso en la medicina empírica. El empirismo, universal o particular, se desintegra únicamente mediante la creación del método científico. Así lo demuestra la evolución histórica de la medicina desde los tiempos hipocráticos hasta el presente. Una ojeada a través de las páginas de la historia médica enseña claramente que el nivel médico-asistencial de cada país, de cada localidad, ha coincidido sin excepción con la calidad de su enseñanza de la medicina y la altura de su investigación, en los aspectos varios, que oscilan entre las ciencias biológicas fundamentales y las observaciones clínicas sistematizadas. Es tan sólo en función de dicha dependencia que la institución de grandes complejos asistenciales resulta eficaz, pues la depuración de la medicina clínica, como de cualquier otra de las ciencias aplicadas, debe realizarse mediante el concatenamiento armónico de su desarrollo tecnológico e intelectual. Ambos elementos evolucionan en un orden lógico de dependencia. Sin tales fundamentos la adquisición de estructuras asistenciales complicadas, así como la importación esporádica de valores individuales, resultan fortuitos e intrascendentes.

De ahí la necesidad de estimular el desarrollo teórico de nuestras escasas instituciones dedicadas a la enseñanza de la medicina o de las ciencias relacionadas, y de fomentar la creación de nuevas facilidades en el medio universitario y en el hospitalario.

La enseñanza, sin embargo, no puede permanecer independiente y entera-

mente responsable de la formación profesional del médico. La enseñanza se nutre de la investigación. Sin ésta se debilita y hunde irremediablemente en la mediocridad y la anodinia. El maestro y el investigador, uno en otro tiempo, se han desdoblado de un modo cada vez más definido, a la par que los fenómenos biológicos se someten a perspectivas más distantes, que las verdades de la biología moderna se quiebran más y más en innumerables facetas. Ambos individuos juegan un papel igualmente fundamental en la enseñanza. El investigador observa e interpreta los hechos biológicos desde un plano de percepción especializado, necesariamente limitado. El maestro aúna las observaciones, las interpreta desde un punto de vista inmediato, las aplica y las transmite. Ambos individuos se influyen mutuamente en su actitud científica, en el hallazgo incesante de nuevas perspectivas, y en último término determinan el nivel científico de la medicina en su conjunto.

El futuro de la investigación médica, por ende de la enseñanza de la medicina, en nuestro círculo profesional no se vislumbra muy halagador. De un lado la atracción ejercida por las grandes instituciones estadounidenses hacia los individuos con capacitación reconocida o potencial para la investigación; de otro la falta de iniciativa gubernamental y privada en la adopción de normas encaminadas a crear un terreno propicio al florecimiento de la medicina académica en sus múltiples aspectos. Las limitaciones presupuestarias resultan abrumadoras, y aún más abrumadora, la rigidez del sistema administrativo educacional. La responsabilidad de la administración universitaria, para citar un ejemplo, empieza y termina con el educador médico y sus necesidades, entendiéndose por tal al profesional encargado de transmitir la información científica existente. Sólo dicho elemento se considera parte integral, por tanto esencial, de la estructura universitaria. La investigación constituye un elemento accidental, sus escasos genuinos promotores y mantenedores, dependientes de la iniciativa propia y del entendimiento de círculos ajenos, resultan inaccesibles al planteamiento administrativo. Paradójicamente, la mera existencia de los principales puntales de la educación médica del país depende en gran parte de la sobrevivencia de tales elementos circunstanciales, no sólo ya en lo científico, sino también en lo económico.

No nos proponemos analizar aquí las virtudes y defectos de normas existentes. Suponemos que fueron creadas a tono con las necesidades y posibilidades del momento. Tampoco pretendemos competir con los versados en el planteamiento administrativo, pues sabemos que sus decisiones se hallan respaldadas por la rigurosa exactitud de sus computadoras. Ante tal inflexibilidad se sobrecoge nuestro espíritu, educado en la versatilidad de los fenómenos naturales.

En el futuro de nuestra medicina científica, nos preguntamos dónde termina de regir el cálculo y dónde comienza el raciocinio.

Ramón Torres Pinedo, M.D.

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El Boletín acepta para su publicación artículos relativos a medicina y cirugía y las ciencias afines. Igualmente acepta artículos especiales y correspondencia que pudiera ser de interés general para la profesión médica.

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Para facilitar la labor de revisión de la Junta Editora y del impresor, se requiere de los autores que sigan las siguientes instrucciones:

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e) Las tablas, notas al calce y leyendas deben aparecer en hojas separadas.

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g) Deben usarse los nombres genéricos de los medicamentos. Podrán usarse también los nombres comerciales, entre paréntesis, si así se desea.

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j) Las referencias deben ser numeradas sucesivamente de acuerdo con su aparición en el texto. Los siguientes ejemplos pueden servir de modelo:

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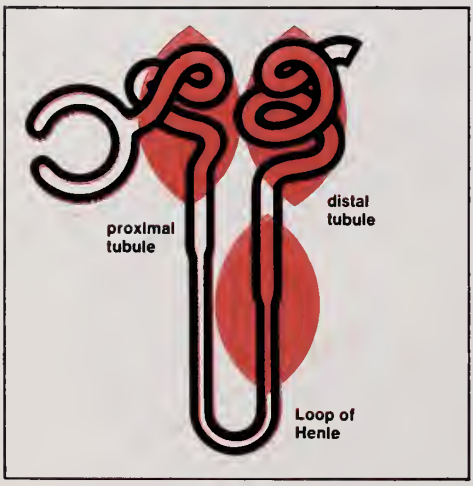

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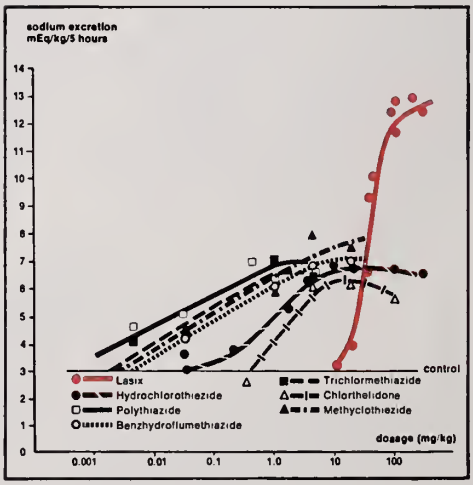
Unlike thiazides, which act only in the proximal and distal tubules, Lasix (furosemide) acts in the loop of Henle, as well as in the proximal and distal tubules



outstanding control of diuresis

prompt, predictable, dose-regulated action—beyond the ceiling of any thiazide[5,6,7,8]

The natriuretic action of Lasix (furosemide) in rats compared with that of various other diuretics (after Timmerman, *et al.*[5])



prompt onset, short duration

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"In our hands, [Lasix] furosemide proved to be a safe and effective diuretic with excellent patient acceptance. Particularly the predictability of response to the drug in terms of its rapid onset and short duration of action enabled us to 'tailor', so to speak, the diuresis to the individual patient's life circumstances. By administering the second dose early in the afternoon, nocturia could be avoided, and the patient assured of a good night's sleep."[9]

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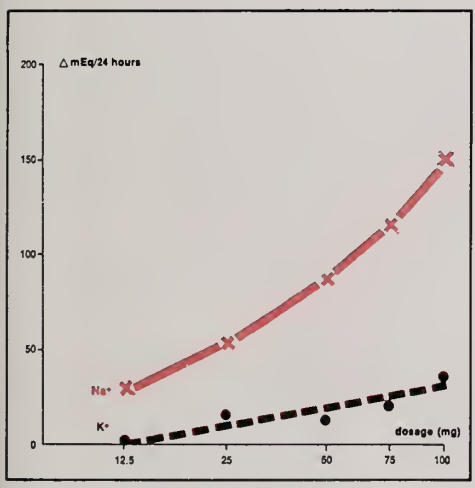
highly favorable urinary Na/K ratio

greatly enhanced Na, proportionately low K excretion[6,7,10]

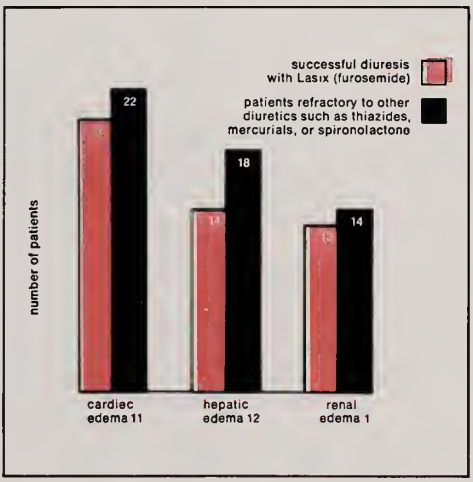
useful in a wide range of patients

in cardiac, hepatic, and renal edema, including thiazide-refractory cases[1,11,12]

Dose-response curve on sodium and potassium excretion in normal subjects after oral administration of Lasix (furosemide) (after Kleinfelder[7])



Response to Lasix (furosemide) in patients refractory to other diuretic agents: results from three studies[1,11,12]



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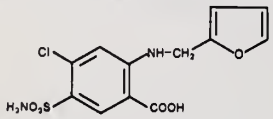
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WARNING—Lasix (furosemide) is a new, potent diuretic, which if given in excessive amounts can lead to a profound diuresis with water and electrolyte depletion. Therefore, careful medical supervision is required and dose and dose schedule have to be adjusted to the individual patient's needs. (See under "Dosage and Administration.")

Lasix (furosemide) is a new diuretic, chemically distinct from the organomercurials, thiazides and other heterocyclic compounds. It is charecterized by: a high degree of efficacy; e rapid onset of action; e comparatively short duration of action; a ratio of minimum to maximum effective dose higher than 1:10; the fact that it acts not only at the proximal end distal tubule but elso et the ascending limb of Henle's loop.

Chemistry—Lasix (furosemide) is an anthrenilic acid derivative. Chemically, it is 4-chloro-N-furfuryl-5-sulfamoylanthranilic acid. The structural formula is as follows:



Indications—Lasix (furosemide) is indicated for the treatment of edema essociated with congestive heart failure, cirrhosis of the liver, and renal disease, including the nephrotic syndrome. Lasix (furosemide) is particularly useful when en agent with greater diuretic potential than those commonly employed is desired. Until further clinical experience is eccumulated, Lasix (furosemide) is not recommended for use in hypertension.

Dosage and Administration—The usual dose of Lasix (furosemide) is 1 to 2 tablets (40 to 80 mg) given as a single dose, preferably in the morning. Ordinarily, a prompt diuresis ensues. Depending on the patient's response, e second dose can be administered 6 to 8 hours later. This dosage and dosage schedule can then be maintained or even reduced. If the diuretic response with a single dose of 1 to 2 tablets (40 to 80 mg) is not satisfactory, e.g., in e patient with congestive heart failure refractory to maximal doses of thiazides, the following schedule should be used: Increase this dose by increments of 1 teblet (40 mg) not sooner than 6 to 8 hours efter the previous dose until the desired diuretic effect has been obtained. This individuelly determined single dose should then be given once or twice delly (e.g., at 8:00 a.m. end 2:00 p.m.). Based on completed studies, a maximum delly dose of 200 mg should not be exceeded. Higher doses ere currently under investigation. The mobilization of edema may be most efficiently and safely accomplished by utilizing an intermittent dosage schedule in which the diuretic is given for 2 to 4 consecutive days each week. With doses exceeding 80 mg/day end given for prolonged periods, careful clinicel and laboratory observations are particulerly advisable. Until further experience in children is accumulated, Lasix (furosemide) should not be given to children.

Contraindications—Lasix (furosemide) is contraindicated in anuria. If increasing ezotemia end oliguria occur during treatment of severe progressive renal disease the drug should be discontinued. In hepetic coma end in states of electrolyte depletion, therepy should not be instituted until the basic condition is improved or corrected. Lasix (furosemide) is contraindicated in patients with e history of hypersensitivity to this compound.

Supplementary Warnings—Excessive diuresis may result in dehydration and reduction in blood volume, with circulatory collapse and with the possibility of vascular thrombosis and embolism particularly in elderly patients. Excessive loss of potassium in patients receiving digitalis glycosides may precipitate digitalis toxicity. Care should also be exercised in patients receiving potassium depleting steroids. Frequent serum electrolyte, CO_2 and BUN determinations should be performed during the first few months of therapy and periodically thereafter and abnormalities corrected or the drug temporarily withdrawn. **In patients with hepatic cirrhosis and ascites initiation of therapy with Lasix (furosemide) is best carried out in the hospital.** Sudden alterations of fluid and electrolyte balance in patients with cirrhosis may precipitate hepatic coma; therefore, strict observation is necessary during the period of diuresis. Supplemental potassium chloride and, if required, an aldosterone antagonist are helpful in preventing hypokalemia and metabolic alkalosis. As with any new drug, patients should be observed regularly for the possible occurrence of blood dyscrasias, liver damage, or other idiosyncratic reactions. In those instances where potassium supplementation is required, coated potassium tablets should be used only when adequate dietary supplementation is not practical. There have been several reports, published and unpublished, concerning nonspecific small bowel lesions consisting of stenosis with or without ulceration, essociated with the edministration of enteric-coated thiezides with potassium salts. These lesions may occur with enteric-coated potassium tablets elone or when they are used with nonenteric-coated thiazides, or certain other oral diuretics. These smell bowel lesions have caused obstruction, hemorrhage, and perforetion. Surgery wes frequently required, and deaths have occurred. Besed on a large survey of physicians end hospitals, both American end foreign, the incidence of these lesions is low, and a ceusal relationship in men hes not been definitely established. Available information tends to implicate enteric-coated potassium salts although lesions of this type also occur sponteneously. Therefore, coated potessium-containing formulations should be edministered only when indicated, end should be discontinued immediately if abdominal pain, distention, nausea, vomiting, or gastrointestinel bleeding occur.

Usage in Pregnancy—The use of eny drug in pregnancy, lactation or in the childbearing age group requires that the potential benefits of the drug be weighed egainst possible hazards to the mother and child. Reproduction studies with Lasix (furosemide) in mice, rabbits, and rats have produced no evidence of drug-induced fetal abnormalities. However, Lasix (furosemide) has had only limited use in pregnant patients.

Precautions—As with any potent diuretic, electrolyte depletion may occur during therapy with Lasix (furosemide), especially in patients receiving higher doses and a restricted salt intake. Electrolyte depletion may manifest itself by weakness, dizziness, lethargy, leg cramps, anorexia, vomiting, and/or mental confusion. In edematous hypertensive patients being treated with antihypertensive agents, care should be taken to reduce the dose of these drugs when Lasix (furosemide) is administered, since Lasix (furosemide) potentiates the hypotensive effect of antihypertensive medications. Asymptomatic hyperuricemia can occur and gout may rarely be precipitated. Reversible elevations of BUN may be seen. These have been observed in association with dehydration which should be avoided, particularly in patients with renal insufficiency. Although no pronounced effect on carbohydrate metabolism has been demonstrated, periodic checks on urine and blood glucose should be made in diabetic patients receiving Lasix (furosemide). Occasional increases in blood glucose have occurred during therapy with Lasix (furosemide). Sulfonamide diuretics have been reported to decrease arterial responsiveness to pressor amines and to enhance the effect of tubocurarine. Great caution should be exercised in administering curare or its derivatives to patients undergoing therapy with Lasix (furosemide), and it is advisable to discontinue Lasix (furosemide) for one week prior to any elective surgery.

Adverse Reactions—Infrequent skin rash, pruritus, paresthesia, blurring of vision, postural hypotension, nausea, vomiting, or diarrhea may occur. A single case of thrombocytopenia has been reported in which Lasix (furosemide) was considered to be the causative agent. There have been a few instances of leukopenia and one report of acute pancreatitis elthough reletionship to the drug has not been established. Lasix (furosemide) induced diuresis has occasionally been accompanied by weakness, fatigue, lightheadedness or dizziness, muscle cremps, thirst, end urinary frequency.

How Supplied—Lasix (furosemide) is supplied es white, monogrammed, scored tablets of 40 mg in amber bottles of 100.

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RESUMEN: ACCION E INDICACIONES: Una sola dosis de IMFERON (inyección de hierro dextrán) produce una alza apreciable de la hemoglobina y una serie completa de inyecciones restituye efectivamente los depósitos de hierro. El IMFERON está indicado únicamente en casos diagnosticados de anemia ferropriva, en los que resulta inefectiva o poco práctica la administración de hierro oral. Tales deficiencias de hierro pueden incluir: pacientes en el último trimestre de gestación; pacientes con trastornos gastrointestinales o en vías de recuperación de intervenciones quirúrgicas del tracto gastrointestinal; hemorragias crónicas con pérdidas de hierro continuas y masivas que no responden rápidamente al hierro oral; pacientes refractarios a transfusiones como fuente de hierro; niños con anemia hipocrómica; pacientes en quienes no se puede confiar que tomen hierro oral.

COMPOSICION: El IMFERON (inyección de hierro dextrán) es una solución bien tolerada de complejo de hierro-dextrán que proporciona el equivalente a 50 mg. de hierro elemental por cada cc. La solución contiene 0.9% de cloruro de sodio y su pH varía entre 5.2 y 6. El frasco-ámpula de 10 cc. contiene 0.5% de fenol como preservativo.

ADMINISTRACION Y POSOLOGIA: La dosis, basada en el peso corporal y gramos de hemoglobina en 100 cc. de sangre, varía desde 0.5 cc. para lactantes hasta 5 cc. para adultos, aplicada diariamente, en días alternos, o semanalmente. El requerimiento total en cada individuo es fácilmente determinado mediante la tabla de dosificación contenida en el prospecto. La inyección intramuscular profunda en el cuadrante superior externo de la región glútea, empleando la técnica trayectoria en Z (con desplazamiento lateral de la piel, previo a la inyección), asegura buena absorción y evita la coloración de la piel. Se recomienda una aguja de por lo menos dos pulgadas de largo para el adulto normal.

EFECTOS SECUNDARIOS: La incidencia de efectos secundarios sistémicos y locales es poco común. Puede ocurrir coloración de la piel. Una dosis excesiva, superior a la requerida, puede producir hemosiderosis. A pesar de que las reacciones alérgicas o anafilácticas son rarísimas, se han presentado ocasionalmente reacciones serias; tres reacciones fatales han sido atribuidas al IMFERON (inyección de hierro dextrán). Raras veces se ha reportado urticaria, artralgia, linfoadenopatía, náusea, jaqueca y fiebre. Se recomienda aplicar inicialmente una dosis de prueba de 0.5 cc.

PRECAUCIONES: Si hay reacción de sensibilidad a la dosis de prueba no deberá administrarse el fármaco. El IMFERON (inyección de hierro dextrán) deberá administrarse únicamente por vía intramuscular profunda. La inyección deberá solamente aplicarse en el cuadrante superior externo de la región glútea, y no en el brazo u otras áreas. El riesgo de carcinogénesis en seres humanos es insignificante cuando se emplea el IMFERON (inyección de hierro dextrán) en la forma recomendada.

CONTRAINDICACIONES: El IMFERON (inyección de hierro dextrán) está contraindicado en pacientes con sensibilidad comprobada al complejo de hierro dextrán. Por estar destinado exclusivamente a la terapia de las anemias ferroprivas, no deberá utilizarse en el tratamiento de otras anemias.

PRESENTACION: Ampulas de 2 cc. cajas de 10; ámpulas de 5 cc. cajas de 4; frasco-ámpulas de 10 cc. de dosis múltiple.

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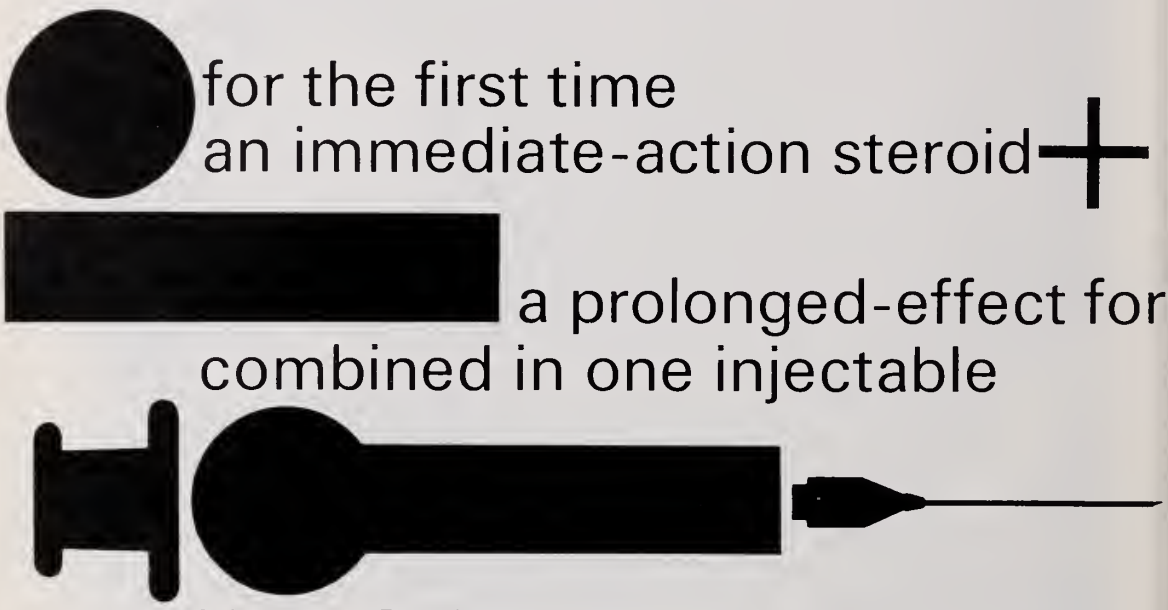
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THE SERUM LIPID PICTURE

A Review

Marta Cancio, Ph. D.

Lipids as components of plasma have been the object of extensive study since the turn of the century. Early studies in this field regarded the lipids in plasma as individual entities. The pioneer studies of the French scientist, M. Macheboeuf, paved the way for a new approach to the study of lipids as regards their state in plasma and their intermediary metabolism. In 1932, and when very little was known on plasma lipids, Macheboeuf (1) concluded that there were two main types of lipoproteins of different stabilities. The accuracy of his statement was proved more than a decade later by a group of Harvard biochemists (2, 3). Since the early 1940's much work has been done on plasma lipoproteins, and all evidence shows that plasma lipids do not exist physiologically as individual chemical entities, but as lipoprotein molecules. Because of this fact, when attempting to study the lipids in plasma, it is much more sound to place emphasis on the study of plasma lipoproteins. The purpose of this paper is to review, in a rather simplified manner, the last advances in plasma lipoproteins, placing more emphasis on their meaning from the metabolic and genetic points of view.

The existence of protein moities capable of combining with large amounts of lipid* to form lipoproteins is now generally accepted. The serum lipids circulate in combination with protein in the form of lipoproteins. These lipoproteins may be classified into lipoprotein classes or families, according to their physico-chemical characteristics (4). In the decade of the 1950's much progress was attained in the characterization of the four major lipoprotein classes, mainly by means of the ultracentrifuge (5, 6, 7, 8, 9). Classification, in increasing order of density class is as follows: the chylomicra of density less than 0.09; the beta lipoproteins of average density 0.98; the beta lipoproteins of average density 1.03; and the alpha lipoproteins of average density 1.12.

A much simpler technique has been developed recently utilizing a modification of existing techniques of paper electrophoresis, by which the four major lipoprotein

From the General Medical Research Laboratory, Veterans Administration Hospital, San Juan, P. R.

** Lipids are insoluble in water, and in order to effect their transport in serum they are attached to protein molecules. There is probably no free lipid in blood, that is, no lipid which is not associated with protein*

classes can also be recognized (10). The main modification to the technic mentioned has been the introduction of 1% albumin to the barbital buffer used for the electrophoretic run. The identification of the various fractions is based on their relative mobilities on paper, just like in the serum protein paper electrophoretic method. The chylomicra, which contain mainly neutral fat of exogenous origin (11), may be recognized because they remain at the place where the sample is deposited on the paper. The beta lipoproteins (low density), migrate with the mobility characteristic of the beta globulins in paper electrophoresis. The very-low density beta lipoproteins (pre-beta lipoproteins) migrate with a slightly larger mobility than the beta-lipoproteins. The alpha lipoproteins migrate with a mobility similar to that of the alpha globulings (Fig. 1).

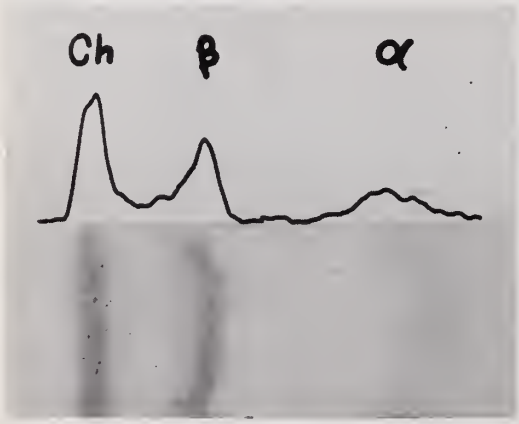


Fig. 1: Electrophoretic pattern showing relative mobilities of chylomicra, beta and alpha lipoproteins (pig serum).

The normal serum lipoprotein electrophoretic pattern will only show a discrete beta-lipoprotein band and a faint alpha-lipoprotein fraction (Fig. 2).

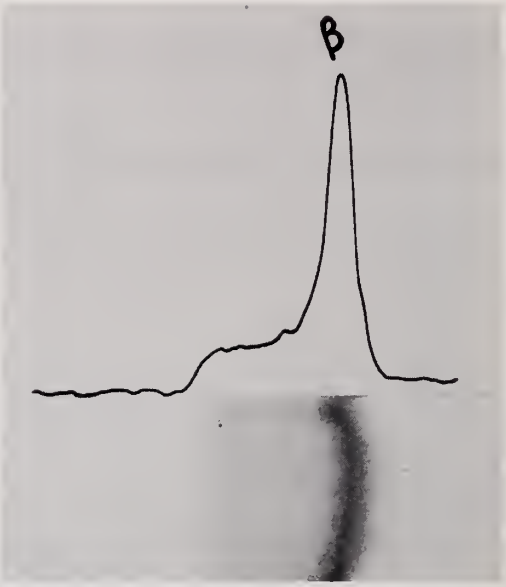


Fig. 2: Normal serum lipoprotein electrophoretic pattern.

However, fluctuations in the amount of the various lipids present in the serum will be reflected in the corresponding lipoprotein electrophoretic pattern obtained. These changes apparently may be explained by the characteristic composition of each of the main lipoprotein fractions.

It has already been mentioned that the chylomicra consist mainly (about 85%) of exogenous triglycerides. Therefore, a marked accumulation in the serum of triglycerides of exogenous origin will be detected as a very dense band at the origin of the electrophoretic strip, in the area of the chylomicra. This pattern is usually associated with a plasma of creamy appearance. It has been postulated that this pattern is characteristic of a rare hereditary biochemical defect consisting of a deficiency of lipoprotein lipase (12), a tissue enzyme responsible for the clearance of exogenous glycerides. This kind

of hyperlipemia has been labelled as "Type I" for the sake of simplicity (13). It has been observed, however, that in spite of the heriditary defect, the hyperlipemia responds well to a low-fat dietary regime. For this reason it is also known as "fat-induced" lipemia (14).

All other lipoprotein fractions are of endogenous nature (14). The low density beta lipoproteins contain mainly (about 45%) cholesterol (4). Therefore, an excessive accumulation of cholesterol in the serum will be identified with a heavily staining beta-lipoprotein band. Hyperlipemia of this kind has been designated as "Type II".

The very low density (pre-β) lipoproteins (15) contain (around 50%) neutral fats of endogenous origin, mainly hepatic (11). Therefore, an excessive accumulation in the serum of newly synthesized triglycerides will be detected as a separate pre-beta lipoprotein fraction. Large quantities of this class of lipoproteins may impart a cloudy or even milky appearance to the serum, so that it is of great theoretical as well as practical importance to be able to distinguish this type of hyperlipemia from the exogenous type, *because it will not respond to a low-fat dietary regime.* It has been observed that this type of endogenous hyperlipemia is inducible by high-carbohydrate (low fat) diets. Therefore, the term "car bohydrate-induced" lipemia (14) has been used to distinguish this type of engogenous hyperlipemia. Carbohydrate intolerance and coronary artery disease have been associated with a lipoprotein pattern in which the pre-beta band is distinguishable.

The pre-beta lipoprotein may appear in the electrophoretic pattern in addition to a heavy β - lipoprotein band. Thus the appearance of both beta and pre-beta bands are characteristic of a hyperlipemia in which both cholesterol and triglycerides are elevated in the plasma. This kind of hyperlipemia has been designated as "Type III" (Fig. 3 and 4).

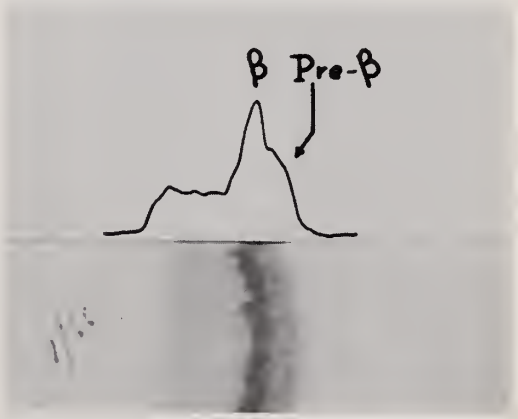


Fig. 3: Electrophoretic pattern showing beta and pre-beta bands.

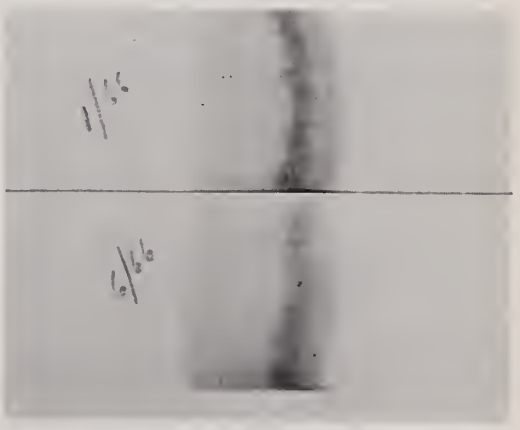


Fig. 4: Electrophoretic patterns of two samples from a type III patient; drawn six months apart.

When the lipoprotein electrophoretic pattern consists of a pre-beta bland alone, the lipemia is designated as "Type IV". This pattern has been associated with coronary artery disease in young adults (15) (Fig. 5).

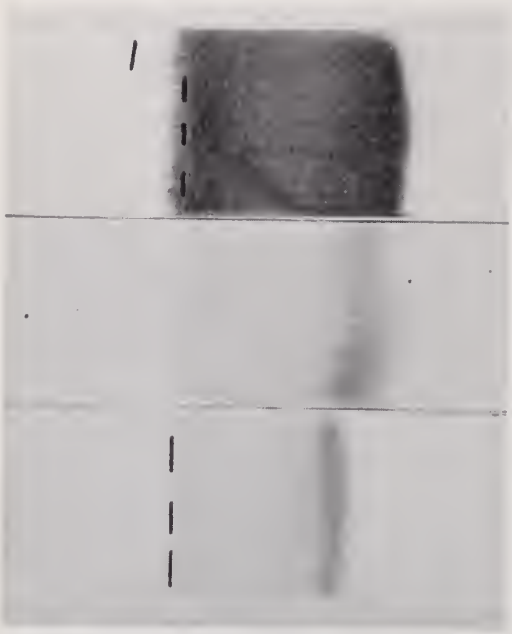


Fig. 5: Top: Type V pattern; center: Type IV pattern; bottom: normal pattern.

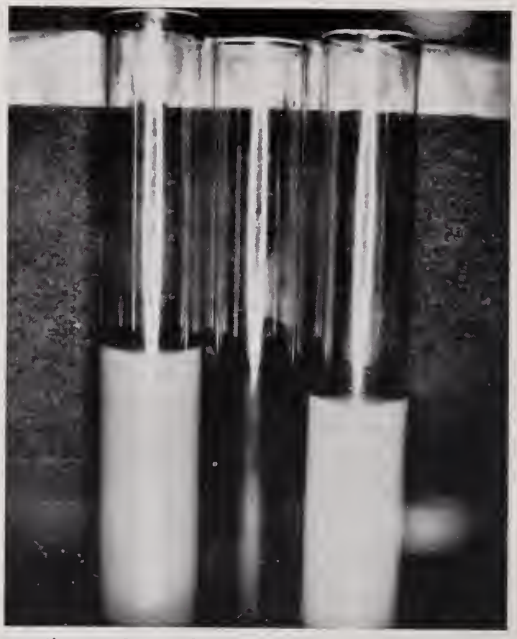


Fig. 6: Sera of creamy appearance from two type V cases. Center: normal serum

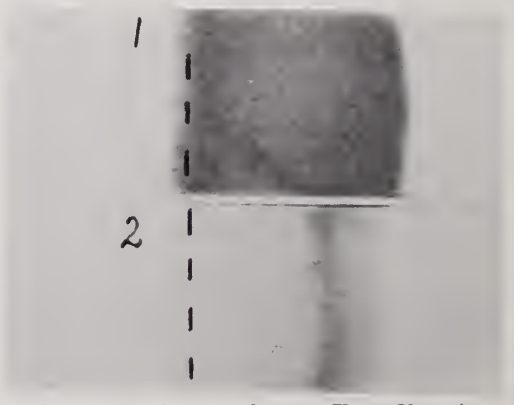


Fig. 7: (1) Pattern from a Type V patient; (2) Pattern from same patient after ten (10) days on a low-carbohydrate, low-fat diet

A pre-beta band in the presence of a heavy chylomicron band is characteristic of hyperlipemia of "Type V" (Fig. 5). The serum in this type of hyperlipemia is of creamy appearance (Fig. 6). This hyperlipemic condition seems to be due to a combined biochemical defect in both fat and carbohydrate metabolism. This pattern has been associated with abnormal glucose metabolism and family history of diabetes. A reduced activity of lipoprotein lipase has also been suggested in this type of hyperlipemia. Hyperlipemia of this type may be induced both by fat and carbohydrate. Improvement seems to occur with restriction of carbohydrates and moderate fat intake (Fig. 7).

Once the type of hyperlipemia is recognized by means of the lipoprotein electrophoretic pattern, it is possible to select the appropriate dietary regime that may be most beneficial in bringing back to normal the serum lipid levels, *regardless of the hereditary nature of the defect* (Table I).

The following is a summary of results

TABLE I: SUMMARY OF HYPERLIPEMIC TYPES

Type	Definition		Association or Significance
	Electrophoretic	*Biochemical*	
I	Increased chylomicron	Increased triglyceride	Deficiency tissue lipoprotein-lipase
II	Increased beta-lipoprotein	Increased cholesterol	Atheromatosis
III	Increased Beta and pre-Beta lipoprotein	Increased cholesterol and triglyceride	Diabetes, Coronary Heart Disease
IV	Increased pre-beta	Increased triglyceride	Coronary artery disease in young men, Diabetes ?
V	Increased chylomicron and pre-Beta	Increased cholesterol and triglyceride	Diabetes Reduced lipoprotein lipase?

obtained by us during the last year while attempting to use the above described procedure for interpretation of the serum lipid picture in the human*.

Serum lipoprotein patterns were determined in patients with hyperlipemia by means of paper electrophoresis in albumin-containing buffer. Results were correlated with serum triglycerides (17), β - lipoproteins (18), serum cholesterol (19), serum phospholipids (20), and appearance of serum (clear, cloudy, milky or creamy), in order to classify cases into one of five types according to the system of Fredrickson (13) as described above. In addition, glucose tolerance, family history, family studies, post-heparin lipolytic activity (12), and correlation with clinical findings were performed in cases of interest. Dietary studies were also performed in selected cases.

Eleven patients have been classified as follows: six of Type III (increased beta-lipoprotein accompained by significant quantities of pre-beta lipoprotein), one case of Type IV (increase in pre-beta liprotein alone), and four cases of Type V (increased chylomicrons accompanied by increased pre-beta lipoproteins). Three of the Type III patients are diabetic and have history of



Fig. 8: Top: Type IV pattern; center: Type III pattern; Bottom: normal pattern.

* *With the technical assistance of José M. León, A R. Sala, B. González and B. Calderón and the cooperation of Drs. Julio V. Rivera and J. L. Cianchini and other members of the Research Laboratory and the Medical Staff of the San Juan Veterans Administration Hospital.*

heart disease; two have strong family history of diabetes and heart disease; and one has a fatty liver due to alcoholism. The patient with Type IV pattern is 30 years old (his father of 50 has a Type III pattern and is a diabetic and has heart disease) (Fig. 8). Two of the cases with the Type V pattern are diabetics and the other two have a strong family history of diabetes and heart disease (one is in the 40-50 years bracket, the other is his son, who is in his early twenties) (Fig. 9).

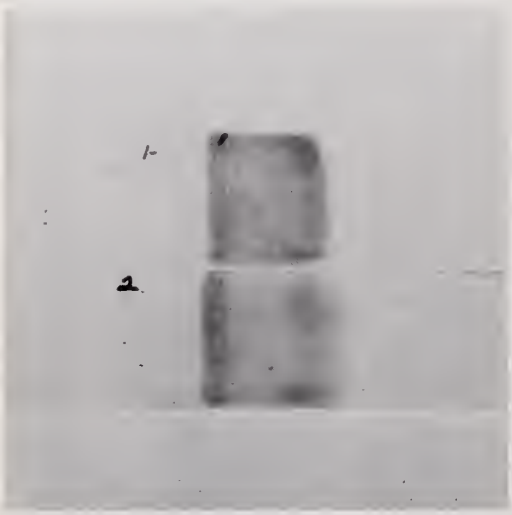


Fig. 9: Patterns of Type V from two members of the same family: (1) son, and (2) father.

Dietary studies in three cases have given promising results which tend to indicate that the serum lipids may become normal if an adequate diet is followed.

It is of interest to note that out of all the sera screened at this laboratory during this year, we have not been able to detect a single case of fat-induced (Type I) hyperlipemia.

Summary

The plasma lipids do not exist physiologically as individual chemical entities, but in combination with protein, in the form of lipoproteins. Therefore, when attempting to study the lipids in plasma, emphasis is given to the study of the serum lipoproteins. Abnormalities in lipids metabolism may be recognized by means of a simple technique for the separation of the Beta lipoproteins (paper electrophoresis in albumin containing buffer). Differentiation of various types of hyperlipemias, (exogenous or endogenous; fat induced or carbohydrate induced), may aid in the nutritional management of the hyperlipemic patient in spite of a hereditary biochemical defect. Some of our results in the study of serum lipids and hyperlipemias are included.

Acknowledgements

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CHRONIC PANCREATITIS
A Review of 257 Cases with Emphasis on Surgical Management

Armando Barreto, M. D.

Few diseases tax the diagnostic and therapeutic skills of the clinician and surgeon more than does chronic pancreatitis. Despite all the theories advanced, the etiology of the disease is still unknown. The clinical manifestations are protean, medical management is rather unsatisfactory and although there is considerable argument regarding surgical therapy this has proven to be the best hope for many of these unfortunate patients.

Our patient population is particulary fitted for a large scale study of this disease. All cases of chronic pancreatitis admitted to the Bronx Veterans Administration Hospital from July 1, 1954 through June 30, 1964 were reviewed. (Table I). The clinical features and the pathological findings determined the type of therapy to be employed. Age, duration of disease, alcoholic intake are important considerations, but most important is the almost universal presence of pain. This pain is chronic and disabling in nature and compels the surgeon, after much hesitation, to perform a surgical procedure.

Most of our cases ocurred in the fourth and fifth decades of life and had the disease from one to ten years (Table II and III).

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Several authors (5) have stressed the importance of differentiating between two clinically different types of pancreatitis, the so called gallstone pancreatitis and alcoholic pancreatitis. In our experience such a differentiation was practically impossible because most patients with chronic pancreatitis and gall bladder disease were in alcoholics. A significant alcoholic history was elicited in 73% of the cases (Table IV). Abdominal pain, the most important clinical feature determining surgical therapy was present in 77% of cases (Table V). Concomitant gall bladder disease ocurred in 16%. Diabetes occurred in a significant number of patients with chronic pancreatitis and this is usually the determining factor in the high morbidity post-operatively. An abdominal mass was palpable in 12 patients and this was invariably a pancreatic pseudocyst all of which required surgery.

Diagnosis

The diagnosis of chronic pancreatitis is made from clinical laboratory and pathological features during investigation of any given case. The serum amylase level is usually elevated during exacerbations of chronic disease but it is not a pathognomonic sign of chronic pancreatitis. It was elevated to

TABLE I: CHRONIC PANCREATITIS

July 1, 1954 - June 30, 1964

Total number of cases	257
Total number of admissions	485
Incidence	0.5%
Operative cases	48 (16.5%)
Operative mortality	5 (10.4%)

TABLE II: AGE DISTRIBUTION

Age	Number	%
20-29	17	6.6
30-39	74	28.8
40-49	86	33.5
50-59	32	12.5
60-69	25	9.7
70-79	7	2.7
Unknown	16	6.2
	257	100.0

TABLE III: DURATION OF DISEASE

Duration	Number	%
less than 3 mos	14	5.8
3-6 months	16	6.2
6 mos.-1 year	12	4.7
1-5 years	78	30.0
6-10 years	41	16.0
11-15 years	16	6.2
16-20 years	9	3.5
unknown	71	27.6
	257	100.0

TABLE IV: ALCOHOLIC HISTORY

	Number	%
Significant	188	73.1
Insignificant	55	21.5
Unknown	14	5.4
	257	100.0

significant levels only in about 50% of the patients (Table VI). Of more diagnostic importance is the presence of calcification in the pancreas which invariably means chronic pancreatitis with greater or lesser degree of ductal obstruction (Table VII). The upper gastro-intestinal series is a valuable adjunct in confirming the presence of an enlarged pancreas or a pseudocyst, but a negative study does not exclude the diagnosis. Organ displacement was present in

TABLE V: CLINICAL FINDINGS

	Number	%
Abdominal pain	197	77
Nausea and vomiting	131	51
Fever	56	22
Jaundice	29	11
Gall blandder disease	42	16
Diabetes	64	27
Abdominal distention	30	12
Abdominal tenderness	142	59
Abdominal mass	12	5
Shock	2	0.8

TABLE VI: SERUM AMYLASE

Units (Somogyi)	Number	%
0-149	50	19.4
150-399	99	38.5
400-699	41	16
700+	6	2.3
Unknown	61	23.7

TABLE VII: X-RAY FINDINGS

	Number	%
Calcification, pancreas	41	16
Organ displacement	52	20
Both	32	12.5
None	114	44.3
Not stated	18	7

20% of cases (Fig. 1). Pancreatography (6) performed by injecting 2cc of Hypaque through a small polyethylene catheter placed in the pancreatic duct during surgery is another valuable diagnostic tool and usually determines the operative procedure to be



Fig. 1: Upper gastrointestinal series showing marked displacement of the stomach secondary to a large pseudocyst of the pancreas.



Fig. 2: Pancreatogram showing normal patency of the duct of Wirsung.

undertaken. It should be a sine qua non in all patients undergoing direct pancreatic surgery. It was performed in a substantial number of operative cases in our series (Fig. 2).

Surgical Management

There were 52 operations performed in 48 patients (Table VIII). In the first group of patients shown in Table VIII the surgical management was mostly directed to correction of gall bladder disease and spasm of the sphincter of Oddi. Obstruction, due to stone or spasm, in patients with so-called common channel (10) whereby both pancreatic duct and common bile duct enter the duodenum jointly undoubtedly accounts for many cases of chronic pancreatitis. This is shown by the fact that correction of biliary tract pathology results in 80 to 90% of good long term results in terms of future attacks of pancreatitis. The most enthusiastic advocators of this surgical approach are Doubilet and Mulholland (1, 2) who reported an eigth year follow-up study of 319 patients on whom cholecystectomy and sphincterotomy was performed. They demostrated a common channel in 316 of these cases and classified 88% of the living patients as having a good result. In our series this indirect surgical approach, that is, surgery in the biliary tract and in the sphincter was performed in 21 cases (44%). Of these, 13 are alive.

The failure of this indirect procedure to relieve a substantial number of patients led different investigators to use a direct approach on the pancreas. The Duval, Longmire, Puestoy and Warren procedures then

TABLE VIII: OPERATIVE PROCEDURES

Operative cases	48
No. of surgical procedures	52
Exploratory laparotomy	6
Cholecystectomy	4
Cholecystectomy & choledochostomy	1
Cholecystectomy, choledochostomy & spincterotomy	12
Choledochostomy alone	2
Cholecysto-jejunostomy	1
Choledocho-jejunostomy	1
Duodenostomy, pyloroplasty & pancreatic biopsy	1
Duodenostomy & exam. of amp.	1
Cysto-jejunostomy (Roux-en-y)	4
Cystogastrostomy	4
Marsupialization	1
External drainage (Penrose)	3
Caudal pancreatectomy	4
Pancreatico-jejunostomy (Roux-en-y)	5
Whipple	1
Pancreatico-lithotomy	1

envolved. Caudal pancreatico-jejunostomy as introduced by Duval in 1954 (3, 4) entails resection of the tail of the pancreas and anastomosis of the resected end of the gland into the jejunum in Roux-en-y fashion. Although this procedure has its place in the surgery of calculous pancreatitis of the tail it fails to provede adequate drainage for the head and body. The recurrence rate of obstruction is high. This procedure was performed in four patients of this series. In 1956 Longmire (8) advocated total pancreatectomy as a definite approach to the problem. This procedure has been largely abandoned because of the high mortality and morbidity involved. Puestoy in 1958 (11) advocated that the pancreatic duct be opened along its entire length and the pancreas then be anastomosed into a defunctionalized loop of jejunum (Roux-en-y). This longitudinal pancreatico-jejunostomy seems to fulfill the basic surgical criteria for correction of the pathologic anatomy and physiology of this disease. It will allow for complete relief of pancreatic obstruction with minimal sacrifice of glandular tissue, return of pancreatic enzymes to the digestive tract and relief of pain (7, 12). Of all surgical methods, this seems to be the best at present. This operation was performed in one patient in our series. Lately Warren (14) has introduced pancreatico-duodenectomy for advanced chronic pancreatitis with multiple obstruction of both ducts in the region of the head of the pancreas. This modality has not been employed in our series.

Pseudocysts of the pancreas were encountered in 12 cases in this series. All these cases followed repeated attacks of chronic pancreatitis and can be listed as complications of such. It is generally agreed that some form of operative treatment is indicated since spontaneous resolution rarely occurs. Excision of the pseudocyst first performed by Bozeman in 1881 is ideal but this is possible only in a small percentage of cases because of the lack of clevage planes for a dissection. This method was not employed in this series. External drainage either by catheter, Penrose or marsupialization is another modality of surgical treatment which was employed here in four cases. Technically it is easier and faster than other procedures and is advantageous in poor risk patients. The mortality in a collective series is as low as 3%. The re-operative rate has run close to 25% (13).

Internal drainage is used to denote an opening between the pseudocyst and a hollow viscus. Cystogastrostomy entails drainage of the cyst into the stomach and was performed in four cases of the series. Cystojejunos-

tomy whereby a loop of the jejunum is anastomosed to the cyst wall in a Roux-en -y fashion was performed in four cases. This method has become more popular in the last ten years (9). The disadvantage is that it is technically more difficult and time consuming when compared to other methods and requires a mature relatively non-friable cyst wall for anastomosis. Caudal pancreatectomy was performed alone in four cases for chronic calculous pancreatitis of the tail of the pancreas. A Whipple procedure ended in an operative death. A case with a big calculus in the duct of Santorini underwent a pancreato-lithotomy (figure 3).



Fig. 3: Roentgenogram showing large calculus in the duct of Santorini.

TABLE IX: FOLLOW-UP

Operative cases	48	
Follow-up as of March 1964	38	(80%)
Deceased from chronic pancreatitis	16	

Follow-up Studies

Thirty eight of the 48 operative cases have been followed. Of the 48 patients operated upon 16 or 33% are deceased. All deaths have been due to chronic pancreatitis or its complications. Of 22 living patients 13 (40%) are asymptomatic (Table IX).

Summary

We have reviewed a large series of cases of chronic pancreatitis with emphasis on operative management. The new methods of surgical therapy have been reviewed. The pathogenesis of chronic pancreatitis is still obscure and thus the surgical therapy is merely directed to the correction of the disabling sequela of the disease.

Resumen

Se ha revisado una serie grande de casos de pancreatitis crónica y hemos enfatizado el manejo quirúrgico. Los nuevos métodos quirúrgicos empleados se han presentado. La etiología de pancreatitis crónica es aún incierta y el manejo quirúrgico se dirige a corregir las complicaciones de dicha enfermedad.

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GRAND ROUNDS: VETERANS HOSPITAL

Edited by: Mario C. Miranda, M. D.

Clinical Abstract

A 57 year old white male was admitted on April 7, 1966 complaining of pain in the sternum since 1964 with the development of a tender mass in that area about a year later. Excision of this was performed in December 1965 and a histological diagnosis of plasmacytoma was made. Radiation therapy was given at another hospital. Otherwise he had been symptomless except for low back pain which dated back to his Army days. Prior to the present admission the patient had pain in both arms and went to another facility where X-rays of the area were taken. Following this the patient sustained a fall with a resultant linear fracture of the right humerus. This prompted his present admission to this hospital.

After being separated from the Army and during his active duty days, the patient suffered from low back pain and was told of the possibility of arthritis of the spine.

The patient was a well developed, well nourished white male in no distress with a long arm cast on the right side. Blood pressure was 130/90 mm Hg. The pulse was 80 per minute and the temperature was 99°F. His weight was 171 lbs. Examination of the chest revealed a well healed surgical scar over the sternal area. Lungs and heart were normal. No organomegaly was noted. Examination of the genitalia, rectum and prostate was normal. No vertebral tenderness could be elicited on percussion. There was slight pain over both scapulae. A small, movable and hard nodule measuring 2 cm in diameter was noted in the lateral aspect of the left thigh. There was no axillary, cervical or inguinal lymphadenopathy. The neurological examination was negative.

The white cell blood count was 8,300/cu. mm. with 62 neutrophiles, 3 bands, 29 lymphocytes, 1 monocyte and 3 eosinophiles. The hemoglobin was 13.5 gms. The hematocrit was 46 per cent. The platelets count was 186,000/cu. mm. The urinalysis was essentially negative, except for traces of albumin. The serum creatinine was 0.5 mg per cent. The sedimentation rate was 22 mm per hour. The blood urea nitrogen was 16.5 mg per cent. The total protein was 7.1 gms, albumin 3.8 gm per cent and globulin 3.3 gm

per cent. The alkaline phosphatase was 6.2 S. J. R. units, the serum calcium 11.1 mg. per cent and the phosphorus 3.95 mg. per cent. The VDRL was non-reactive. Examination for Bence-Jones protein was negative. The stools for ova and parasites revealed *Trichuris trichura.* The clot retraction was complete in two hours.

On April 25, 1966 the patient was placed on melphalan, 2 mgs. three times per day. On May 16, 1966 he developed limping of the left lower extremity. The patient was placed on physiotheraphy regime. On May 31, 1966 melphalan therapy was discontinued. Very little improvement had been observed during the course of this treatment. On June 9, 1966 the patient was started on prednisone, 15 mg daily. The main problem of this patient as of the present date is severe excruciating pain in the low back radiating to the left leg which has required constant use of analgesics and narcotics.

Discussion

Dr. Félix M. Reyes:*

Two biopsies were obtained in this patient. One from the bone marrow and the other from the previously mentioned nodule on the left thigh. The skin biopsy (Fig 1) shows two nodules 5 mm each with large cellular masses. These nodules consists mostly of mature plasma cells with eccentric nuclei and immature forms, probably myeloma cells (Fig. 2). Bone marrow examination shows multinucleated myeloma cells and large amounts of plasma cells. Diagnosis is myeloma of the bone narrow and metastasis to the skin of the thigh.

**Chief, Laboratory Service.*

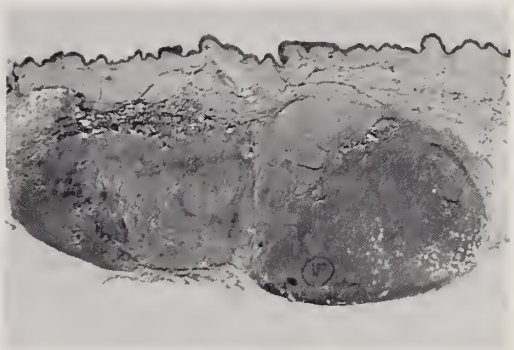


Fig. 1: Biopsy from subcutaneous nodule of the left thigh showing conglomeration of cellular masses (X5, H&E).

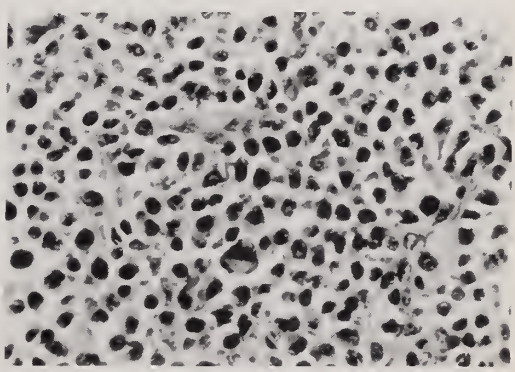


Fig. 2: Higher magnification shows these cellular masses to be chiefly plasma cells and a number of myelma cells (X475, H&E).

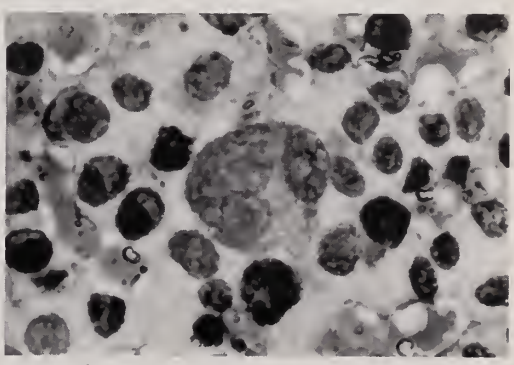


Fig. 3: Bone marrow from lumbar vertebra showing myeloma cells. One in the center with 3 nuclei, others chiefly plasma cells (X1500, H&E).

Dr. Laszlo Ehrlich:**

Review of the outside films taken on April 2, 1966 shows an osteolytic lesion involving the shaft in the upper third of the right humerus. The films taken in this hospital five days later reveal a pathological fracture at the site of he humeral lesion.

In the chest film there is involvement of the ribs by multiple osteolytic lesions. The anterior segment of the right fifth rib is completely destroyed. Skeletal survey, including the dorsal spine, pelvis, lumbar spine and skull show osteolytic lesion in the lateral aspects of the bodies of L_1 and L_2 and also in the left sacro-iliac area and frontal bone. All these osteolytic changes are, of course, compatible with the clinical diagnosis of multiple myeloma.

Dr. Michael B. Shimkin:‡‡

Plasmacytomas represent a subdivision of the lymphomas which include lymphosarcoma, reticulum cell sarcoma and others. As far as incidence is concerned, we see maybe 2,000 to 2,500 cases per year in the United States. So, it is not a common lesion, although recognition of the disease has gone up considerably during the past few years with the recognition of gamma globulin patterns which reveal this disease sometimes before clinical manifestations are apparent.

Multiple myeloma has several distinct features that distinguish it from other lymphomas: the distribution of sexes is about even, it occurs as frequently if not a little bit more so in the Negro population than it does in the white population; and the disease is usually of the aged population, so that most of your patients will be certainly 50 years or up. This disease is the result of a neoplastic process involving the plasma cells.

Since there is a gradient between normal plasma cells and neoplastic cells, misdiagnosis of other lesions resembling plasmacytoma are not too uncommon. These errors often occur in the nasopharyngeal area where the lesions are readily amenable to radiotherapy. Long term follow-ups show a so-called "cure", in these cases. Reviews of hospital collections of nasopharyngeal plasmacytomas show that many of these are not tumorous at all. They are reactive types of granulomas with many plasma cells.

A frequent complication of multiple myeloma is the so-called myeloma kidney. The first sign of such involvement is a rise in blood urea nitrogen. The patients that do not die a renal death fall prey to secondary infections despite the high levels of globulin. These are incompetent globulins from the immunological standpoint. Unusual types of pneumonia such as Friedlander's which are not commonly encountered in the general population are observed in these patients.

The extramedullary types of myeloma infiltration are not too uncommon if you look for them. For example, in many patients with bony involvement with multiple myeloma, if you look carefully over their skull with your hands and over the skin, you will detect subcutaneous nodules, some that do not bother the patient at all. They are incidental findings at most, yet if you wish to follow this through with biopsy, it would not be unusual to have this shown

**Chief, Radiology Service.*

‡‡*Chief of Cancer Biology of the Fels Research Institute and Professor of Medicine, Temple University School of Medicine.*



Fig. 4: X-ray of the right humerus showing fracture at the shaft thru one of the osteolytic lesions.

to be an infiltrate like the one in this patient was. They are not necessarily connected with bone.

Another terminal picture which is sometimes seen is a myeloma leukemia with the appearance of the myeloma cells in the blood stream. We have seen patients with 16 to 20% myeloma cells in the peripheral blood. This is incidental to dissemination of the disease by the hematological route.

As far as treatment is concerned, there is really no adequate treatment for multiple myeloma. I would like to recall to you that this is an X-ray sensitive tumor and the initial handling of this situation should be roentgen therapy, particularly if you have a target to shoot at. Radio-therapy has the advantage that you can localize your treatment rather than exerting your effect systematically. However, these patients eventually require some sort of generalized treatment and this is where the alkylating agents come into role. I am not particularly happy with phenyl-alanine mustard compounds. These are toxic drugs which have a profound effect on the platelets. The most commonly used are Alkeran and Cytoxan, Alkeran being the more toxic of the two compounds. Good results in the treatment of multiple myeloma by our criteria means an improvement in immunological status, no new lesions and no progression of the present ones, reduction of the plasma cells to 5 to 10% and disappearance of abnormal plasma cells from the bone marrow. It is very difficult to see improvement in these patients if we are depending upon X-ray changes because these are pretty well established and it takes a lot of therapy to reverse the X-ray deformities. Among the first things that you see is a clinical improvement of the patient with a sensation of well being. Secondly, a reduction in the abnormal globulin in the plasma is observed. This is followed by an improvement in the hematopoietic system as manifested by slow recovery of the hemoglobin values. It is important to remember that with alkylating agents it is just as easy to get the reverse-to reach toxic levels where a reduction in hemoglobin and platelet count is the result of your treatment and that no improvement in the patient is observed.

It is very difficult to tell if this patient

had multiple myeloma dating back to many years and was called something else. This is not uncommon. He is apparently on a terminal phase with extramedullary spread of the disease. In terms of systemic therapy, I agree with the use of prednisone and testosterone as you have been doing until now. Radiotherapy could give gratifying results specially if utilized on the neoplastic lesions of the spine. Incidentally, in neoplastic lesions involving the spine always look much higher than you would expect the symptoms to arise from. For example, in patients having fairly low back pain due to metastatic disease, do not overlook the possibility that the main metastasis may be as high up as the cervical spine. There is a very poor relationship between the X-ray evidence of involvement and the site that you anticipate from the neurological examination. This is just a sketch of some of the things of multiple myeloma that occurred to me during the discussion of this case. Are there any specific questions?

A doctor:

Have you encountered patients with prominent hypercalcemia? How have you handled them?

Dr. Shimkin:

Yes, of course, this should have been mentioned before. Hypercalcemias are quite frequent in multiple myeloma. Prednisone is usually sufficient to handle this situation. Patients have respondered fairly well to this kind of therapy in most of the cases that I have handled. Of course, if the hypercalcemia is so severe as to lead into mortality, this is a very benign way to die. Certainly the patient with tremendous pain and hypercalcemia which you cannot control goes smoothly into coma and passes out in a very peaceful condition.

A doctor:

Has disease similar to myeloma been produced in animals?

Dr. Shimkin:

Several strains of mice been shown to develop plasmacytomas following an injection of a wide variety of materials. Those plasmacytomas have been very interesting experimental media for the various phases of research. In the first place, they do respond to many of the drugs used clinically for multiple myeloma so that they can be

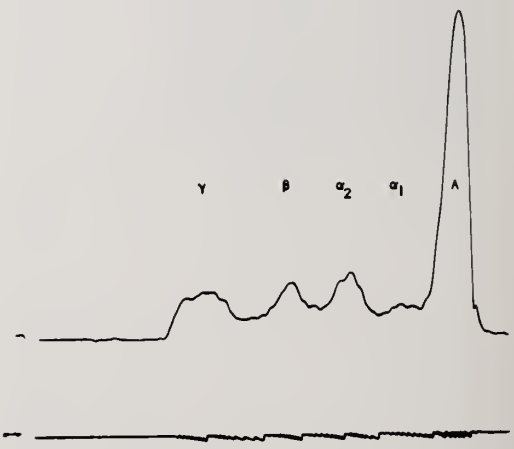


Fig. 5: Serum protein electrophoresis showing increase in alpha-2 globulin. Fractionation as follows:

α	β	α_2	α_1	Alb.	
16	16	16	7	65	120
13.33	13.33	13.33	5.83	54.18	100%
				A/G — 1.18	

used as a screening device. Secondly, they provide very rich material for more basic studies of gamma and other globulins which are produced in this condition. Interestingly enough, the experimental plasmacytomas in animals do not have an overall increase in all the globulins, but are usually manifested by abnormal rise of a very specific component. This is interpreted as evidence that the tumor arises from some sort of mutational change, essentially of one cell. If many cells were involved, we would expect a rise in the general pattern of all the globulins, in some way resembling the normal situation.

Editor's Note:

A striking feature in multiple myeloma is the evidence of disturbance in protein synthesis. Hyperproteinemia, commonly noted in these patients, is due to an increase in the globulin fraction in practically all cases. Abnormal components in the general range of gamma globulin mobility and the presence of an "M fraction" with intermediate mobility between beta and gamma are most frequent. Electrophoresis in this patient failed to show any of these characteristics (Fig. 5). It only shows an increase in the alpha-2 globulin fraction and a slight decrease in gamma fraction.

INFORME ANUAL DEL PRESIDENTE DE LA ASOCIACION MEDICA DE PUERTO RICO A LA CAMARA DE DELEGADOS

Luis F. Sala, M. D.*

San Juan, Puerto Rico
12 de noviembre de 1966

Presentaré este informe en tres partes principales:

1) Resoluciones aprobadas por la Cámara de Delegados en nuestra reunión de septiembre de 1966;

2) Gestiones que consideramos de importancia en nuestra presidencia;

3) Recomendaciones y sugerencias para que las conserven en sus pensamientos durante las deliberaciones que habrán de seguir en este y años futuros.

Primera Parte

Las siguientes resoluciones fueron aprobadas por la Cámara de Delegados celebrada el 10 de septiembre de 1966:

Resolución Núm. IX-66-1 y IX-66-2: Estas dos resoluciones contienen enmiendas al reglamento de la Asociación Médica de Puerto Rico y, por lo tanto, fueron referidas al Comité de Resoluciones y habrán de ser discutidas más tarde en los trabajos de esta Cámara.

Resolución IX-66-3: Esta resolución contiene una reafirmación de parte de esta Cámara en otra resolución previamennte aprobada, ambas en relación a la aprobación de programas de internado y residencias por el Tribunal Examinador de Médicos. Copia de esta resolución ha sido enviada al Presidente del Tribunal Examinador de Médicos, además de haberse discutido personalmente el asunto con él.

Resolución IX-66-4: A través de esta resolución la Cámara dio reconocimiento al mérito de nuestro Secretario Ejecutivo, Sr. Jorge A. Ramírez.

Resolución IX-66-5: Médicos transeuntes a reunión anual. Hemos dado instrucciones al personal administrativo de la Asociación Médica de Puerto Rico para que implemente el acuerdo de esta resolución durante el transcurso de la presente convención.

Resolución IX-66-6: Radiólogos, urólogos y ortopedas. Esta resolución fue referida a nuestros asesores legales para ser discutida nuevamente durante las sesiones de esta Cámara. La opinión de nuestros asesores legales aparece incluída en el manual del Delegado.

Resolución IX-66-7: Dr. Diego Alvarez Chanca. Esta resolución ha sido debidamente implementada y el próximo sábado 19 de noviembre, a las 5:00 p.m., se llevará a cabo, en los jardines de la Asociación Médica, la develación del monumento al doctor Alvarez Chanca.

Resolución IX-66-8: Colegiación y la Asociación Médica. Esta resolución ha sido referida al Consejo Judicial y Administrativo para su consideración. (Aprovechamos esta oportunidad para informar a los compañeros que el Presidente de este Consejo, Dr. Walter J. Benavent, ha estado enfermo de algún cuidado últimamente, por lo que no nos podrá acompañar durante los actos de esta convención. Hacemos votos por el pronto restablecimiento del compañero Benavent.)

Resolución IX-66-9: Esta resolución abre las puertas del edificio de la Asociación Médica para albergar a los compañeros de la Asociación Puertorriqueña de Graduados en Universidades Españolas. Le hemos indicado a los compañeros que tan pronto estén en condiciones de implementar

* *Presidente, Asociación Médica de Puerto Rico, 1966.*

dicha resolución se acerquen a nosotros para hacer las gestiones pertinentes.

Resolución IX-66-10: Hospital Presbiteriano. Esta resolución fue referida al Consejo de Servicios Médicos, quien está haciendo la investigación correspondiente sobre este asunto.

Resolución IX-66-11: Compañerismo, condolencia. Esta resolución fue referida a la Junta de Auxilio Médico Mutuo para su estudio y recomendación pertinente. También ha sido implementada centralmente y a través de los distritos.

Resolución IX-66-12: Al igual que la Resolución 1 y 2, la resolución Núm. 12 constituye una enmienda a nuestro reglamento y será objeto de discusión posteriormente en las deliberaciones de esta Cámara.

Resolución IX-66-13: Nos hemos comunicado con la compañía telefónica de Puerto Rico expresándole el sentir de la Cámara de Delegados con respecto al modo en que debe aparecer el nombre de la Asociación Médica de Puerto Rico en la guía telefónica.

Resolución IX-66-14: A través de una carta a toda nuestra matrícula, informamos sobre la creación del Socio Protector. Nuestro tesorero informará más adelante del resultado de esta gestión.

Resolución IX-66-15: Esta resolución hizo nuestra la Núm. 14-A-66, aprobada por la Cámara de Delegados de la Asociación Médica Americana en su reunión de junio de 1966. El propósito de esta resolución es la de estimular la participación del médico como miembro de las juntas de directores de hospitales. Como un modo de implementar esta reslución en Puerto Rico, la Asociación Médica de Puerto Rico co-auspició un seminario sobre hospitales en relación al cual daremos detalles más adelante en este informe.

Resolución IX-66-16 y IX-56-17: Estas dos resoluciones quedaron presentadas en nuestra reunión pasada, formando parte del informe del Consejo Judicial y Administrativo. Más adelante en esta Cámara tendremos oportunidad de deliberar sobre ellas, ya que constituyen enmiendas al Reglamento. La primera se refiere al Comité de Resoluciones y la segunda al Comité de Finanzas.

Resolución IX-66-18: Esta resolución contiene el plan de escalonamiento de cuotas que formaba parte del informe del Consejo de Relaciones Públicas. Debido a que también constituye enmiendas a nuestro Reglamento, dicho plan quedó presentado en nuestra pasada reunión y será objeto de deliberación durante los trabapos de esta Cámara.

Otras resoluciones pendientes:

Resolución XI-65-17: Esta resolución pide una evaluación de la legislación existente que afecta la práctica de la medicina en Puerto Rico y la salud en general de nuestro pueblo. En este trabajo estamos siendo ayudados por nuestros asesores legales. Ya se han sometido enmiendas al Hon. Secretario de Salud sugiriendo que se incorporen al reglamento de hospitales.

Resolución XI-65-18: Esta resolución se refiere a la obtención del examen para graduados de medicina en universidades extranjeras. Durante el transcurso del año hemos tenido conversaciones con diferentes representates del ECFMG. Durante el próximo mes de diciembre haremos una presentación formal ante la Junta de Directores de dicha organización.

Resolución XI-65-22: Esta resolución se refiere a la orientación que debe ofrecer la Asociación Médica a grupos o entidades interesados en establecer o mejorar hospitales de la comunidad en Puerto Rico. En estas gestiones hemos tenido la valiosa ayuda de nuestro asesor de hospitales, el Sr. José Rivera Escalona. Como parte de vuestro manual del Delegado aparece un informe del señor Rivera Escalona referente a este asunto.

Resolución XI-65-33: Esta resolución pide que se realice una evaluación de los planes de servicio de salud operantes en Puerto Rico. El Consejo de Servicios Médicos, dirigido por el Dr. José A. Alvarez de Choudens, ha trabajado activamente cumplimentando esta resolución. Podemos decir con satisfacción que son varios los planes o entidades que contratan con planes que se han acercado a la Asciación Médica a solicitar su consejo y asesoramiento en este campo.

Resolución XI-65-40: Esta resolución pedía el auspicio para prohibir el maltrato físico de los niños por sus padres. Recientemente el Dr. Egidio S. Colón Rivera nos representó en conversaciones con los dirigentes de la División de Bienestar Público para estudiar un anteproyecto que habrá de ser presentado a la Legislatura sobre este asunto.

Resolución IV-66-1: Esta resolución presentaba una recomendación a la SSS referente a la in-

corporación en su cubierta de servicios psiquiátricos. Hemos sido notificados por el Director Ejecutivo, Sr. Pedro J. Ortiz Aponte, que próximamente se incluirán estos servicios dentro de la cubierta de los empleados federales en forma experimental.

Resolución IV-66-2: Esta resolución solicitaba el estudio de la práctica de varias instituciones que emplean médicos a sueldo. Los Consejos de Servicios Médicos, y Judicial y Administrativo, han seguido trabajando en este asunto, teniendo conversaciones con representantes de diferentes hospitales que utilizan esta práctica. Podemos decir con satisfacción que dichas instituciones están seriamente estudiando la manera de eliminar dicho método de sus operaciones.

Resolución IV-66-8: Esta resolución solicitaba el establecimiento de grupos de extensión para personal de salud pública y medicina administrativa. Al comenzar el presente año escolar se inauguró dentro de la Facultad de Medicina de la Universidad de Puerto Rico el curso tendiente a conceder la maestría en administración de hospitales. Los estudiantes de este curso fueron invitado de la Asociación Médica durante la celebración del Seminario de Hospitales el 25 de octubre.

Resolución IV-66-15: Esta resolución pide la obtención de estadísticas sobre utilización de servicios de caridad por individuos solventes. Continuamos haciendo gestiones ante el Concilio de Salud, la Asociación de Hospitales y la Asociación de Administradores de Hospitales para que esta información sea producida y presentada a las autoridades gubernamentales competentes. Este es un aspecto de nuestro trabajo que debemos enfatizar y continuar presentando los datos que se obtengan a los dirigentes de nuestras ramas ejecutivas y legislativas.

Segunda Parte

Actividades importantes:

I. *Administración:*

En el año transcurrido continuamos la labor de mejorar la administración interna de nuestra Asociación. Aunque hemos tenido algunos cambios de personal, nuestra organización camina con mayor seguridad y poco a poco continuará adquiriendo la eficiencia necesaria para hacer menos ardua la labor de los oficiales de la Asociación. La innovación principal y que pronto habrá de ponerse en práctica, lo es el cambio en la manera de estructurar nuestra contabilidad del modo conocido como "cash basis" al sistema "accrual". En este trabajo hemos tenido el valioso asesoramiento de nuestros auditores externos, la firma de Haskins & Sells, en especial del Sr. Robert Caballero. Debo agradecer aquí también la excelente cooperación de los doctores. Colón Rivera, Rigau y Bladuell, quienes dedicaron una gran parte de su tiempo a atender los problemas financieros de nuestra Asociación.

A partir del 17 de octubre de 1966 adquirimos los valiosos servicios del Sr. Daniel F. Rigau, quien ocupará la posición de Vicepresidente Ejecutivo de la Asociación Médica de Puerto Rico sustituyendo al Lic. Francisco A. Colón, quien habrá de dedicarse a la práctica privada de su profesión.

II. *Relaciones con nuestro gobierno:*

Durante el pasado año hemos procurado establecer relaciones cordiales con diferentes oficiales de nuestro gobierno con el propósito de hacerle llegar el interés de la Asociación Médica en cooperar para resolver los problemas de salud de nuestro pueblo, pero a la misma vez haciéndoles entender que la filosofía de nuestra Asociación comprende varias premisas principales, tales como la libre selección de médico y paciente que ofrecen al ciudadano el servicio médico y hospitalario que necesitan en una forma digna y responsable. Además de las visitas hechas a nuestro Honorable Gobernador, y sobre la cual informamos en nuestro informe pasado, hemos conversado en varias ocasiones con el nuevo Secretario de Salud, Dr. Mario Rubén García Palmieri, quien sabemos hace suyas las preocupaciones de esta Asociación. Entrevistas similares han sido sostenidas con el

Ayudante Especial del Gobernador Sr. Juan Fernández; con el Sr. Antonio Cuevas Viret, Director de la Oficina de Personal; el Lic. Rafael Hernández Colón, Secretario de Justicia; el Sr. Jorge Font Saldaña, Secretario de Hacienda; el Lic. Alfredo Nazario, Secretario del Trabajo, el Sr. Concepción Pérez Pérez, Administrador del Fondo del Seguro del Estado; y con la Sra. Aida G. de Pagán, Directora de Bienestar Público.

Además, de ponernos en relación con miembros de la rama ejecutiva de nuestro gobierno, hemos procurado, además, relacionarnos con miembros de nuestra Cámara Legislativa y a este efecto hemos celebrado además varias entrevistas con los doctores Antonio Fernós Isern y Pablo Morales Otero, miembros del Senado y Cámara respectivamente. También hemos celebrado conversaciones con los siguientes legisladores: Senador José Arsenio Torres, Senador Luis Negrón López, Representante Antonio Sagardía, Representante Severo Colberg, y Representante Julio Viera Morales.

El Dr. José A. Pereyó ha sido nombrado Presidente de nuestro Comité de Legislación y sobre él recaerá la responsabilidad de ayudar a nuestro próximo Presidente, Dr. Luis A. Izquierdo Mora, a llevar adelante nuestras ideas legislativas para con nuestros legisladores.

III. *Ley Medicare — Su implementación en Puerto Rico:*

En los últimos cinco meses han visto la implementación en Puerto Rico de los Títulos XVIII y XIX de la Ley del Congreso 89-97, conocida como Medicare. Vamos a considerar por separado la aplicación de ambos títulos.

Título XVIII:

Como es de todos conocido, el Título XVIII de la Ley Medicare contiene dos partes básicas: la parte A, que contiene el seguro de hospitalización, y que es compulsoria para todos los beneficiarios de la Ley del Seguro Social; y la parte B, que ofrece el seguro médico para dichos beneficiarios, y que es opcional.

Con relación a la Parte B del Título XVIII, nos sentimos muy orgullosos en poder decir que la Asociación Médica de Puerto Rico fue la única Asociación Médica Estatal dentro del territorio americano que se manifestó públicamente a favor de que sus conciudadanos mayores de 65 años tomaran este seguro médico opcional de manera que pudieran tener la oportunidad de escoger libremente su médico. De un total de 150,000 de nuestros conciudadanos, alrededor de 100, 000 siguieron la recomendación de la Asociación Médica de Puerto Rico aceptando participar en la Parte B del Título XVIII; y cada mes manifiestan nuevamente su respaldo a nuestra Asociación al continuar pagando los $3.00 que corresponden. El tiempo nos ha demostrado que esta vigorosa actuación de la Asociación Médica de Puerto Rico ha sido uno de sus mayores logros en el año transcurrido. Con este gesto un 5% de la población de Puerto Rico pasó de la insolvencia a la solvencia médica y el 89% de los elegibles que votaron lo hicieron a favor de nuestro sistema de medicina.

Título XIX:

La implementación del Título XIX en Puerto Rico podemos decir que es hoy por hoy nuestro problema principal. La importancia y gravedad de dicho problema reside no solamente en lo que pueda ocurrir en el día de hoy sino que aún más importante, las consecuencias que posteriormente pueda tener la implementación de este plan en Puerto

Rico. En la actualidad la implementación del Título XIX niega al ciudadano puertorriqueño su derecho básico que la ley federal le concede. La aplicación del Título XIX en Puerto Rico restringe a nuestros beneficiarios a no escoger a su médico y a su hospital libremente; la aplicación del Título XIX en Puerto Rico obliga al puertorriqueño pobre a seguir recurriendo al servicio de caridad compulsorio e involuntario en instituciones gubernamentales.

Nuestra preocupación por este asunto fue manifestada primeramente al Dr. Guillermo Arbona durante su incumbencia en el Departamento de Salud y posteriormente a su sucesor, el Dr. Mario Rubén García Palmieri. Tanto a nuestro propio Gobernador como a las otras personalidades gubernamentales con quien hemos conversado, hemos expuesto nuestra preocupación por este problema. Ante la incomprensión local, nos hemos visto obligados a llevar nuestra preocupación ante las autoridades federales corespondientes y en dos ocasiones hemos visitado al Sr. Wilbur Cohen, de la Secretaría de Salud, Educación y Bienestar, y a la Comisionada de Bienestar Federal, la Dra. Ellen Winston. Es de sumo interés apuntar que ninguno de estos dos funcionarios tenía conocimiento detallado de la manera que se estaba implementando ni éste ni muchos otros planes federales en Puerto Rico. Ambos nos manifestaron enfáticamente su interés en una implementación correcta de estas disposiciones de la ley en nuestra Isla, manifestándonos sin ambages su deseo de que se cumpla en Puerto Rico la intención legislativa federal de eliminar los servicios médicos y hospitalarios de segunda categoría para los indigentes y ofrecer a toda nuestra población beneficiaria igual calidad de servicios. Las palabras textuales de la doctora Winston fueron: "We want quality, not charity."

En nuestra preocupación por lograr una implementación correcta del Título XIX en Puerto Rico, dedicamos esfuerzos durante el año pasado a lograr que se ofreciera a nuestros conciudadanos la oportunidad de recibir los beneficios de esta ley hospitalizándose no solamente en hospitales gubernamentales sino que también en los hospitales privados. A este efecto y a través de conversaciones con el anterior incumbente del Departamento de Salud, Dr. Guillermo Arbona, auspiciamos la redacción de un contrato a celebrarse entre los diferentes hospitales privados y el Departamento de Salud para el logro de estos fines. Dicho contrato fue aceptado por el Departamento de Salud y se distribuyeron copias entre los diferentes hospitales para que sirvieran de guía en las discusiones individuales de cada hospital con el Departamento de Salud. Nuestros hospitales, carentes de precedente, de orientación y de visión, no supieron aprovechar esta oportunidad que les brindamos. Terminó la oportunidad por el momento con el cese del doctor Arbona en la Secretaría de Salud. Sin embargo con una aplicación adecuada del Título XIX en la cual la agencia administrativa aceptare emancipar al puertorriqueño pobre y le abriera las puertas utilizando los fondos federales según su verdadero propósito, la oportunidad de lograr el intento original, sería mucho más amplio y pleno, ya que incluiría no solamente libre escoger de hospital sino también libre escoger de médico.

La Asociación Médica de Puerto Rico debe continuar muy pendiente y a la vez muy activa en los desarrollos futuros de la implementación de este plan. Nos hemos dado cuenta de que el diálogo necesario para ello es preciso llevarlo a cabo a todas las mentes, desde el Alcalde de Machuchal al Presidente

de los Estados Unidos de América. No hay concesión honrosa posible para la Asociación Médica de Puerto Rico que no sea lograr esta justicia para nuestros conciudadanos.

IV. *Concilio de Salud:*

Conjuntamente con la Asociación de Hospitales de Puerto Rico y la Asociación de Administradores de Hospitales de Puerto Rico, la Asociación Médica de Puerto Rico participó en el pasado año en la creación del Concilio de Salud de Puerto Rico. Esta idea había estado latente durante los últimos años pero ha sido recientemente que se logró hacerla realidad. En la actualidad participan en el Concilio de Salud las siguientes entidades: Asociación de Hospitales, Asociación de Administradores de Hospitales, Colegio de Farmacéuticos, Colegio de Cirujanos Dentales, Asociación de Enfermeras Graduadas, Asociación de Salud Pública de Puerto Rico y la Asociación Médica de Puerto Rico. Ya están los papeles necesarios para incorporar debidamente dicho Concilio en la Secretaría de Estado. Esta deberá llegar a ser de influencia y de beneficio para los mejores intereses de nuestra comunidad. Posteriormente se irán añadiendo otras instituciones interesadas de modo que este Concilio pueda llegar a representar la voz unida de las diferentes profesiones que se entienden con la salud de nuestro pueblo. Pido a esta Cámara de Delegados que den un respaldo sólido al Concilio de Salud de Puerto Rico.

V. *Fondo del Seguro del Estado:*

Es de todos conocido el examen que recientemente hicieran de las actividades del Fondo del Seguro del Estado las ramas ejecutiva y legislativa de nuestro gobierno. Tuvimos la oportunidad de participar en las vistas públicas que en relación al Fondo celebrara la comisión legislativa presidida por el Representante Severo Colberg. En esa ocasión presentamos a nuestros legisladores dos ideas básicas:

1. Reclamamos que los obreros asegurados en el Fondo del Seguro del Estado puedan escoger libremente el médico que habrá de ofrecerles tratamiento. En un buen número de los estados de la Unión Americana se ofrece esta oportunidad a los trabajadores de dichas jurisdicciones. En Puerto Rico se le ofrece a los trabajadores en proyectos federales. Deseamos que se le ofrezca a trabajadores en proyectos puertorriqueños.

2. Señalamos a la comisión investigadora las limitaciones que para el paciente constituye el atar al médico que trabaja para el Fondo a un horario específico, creando en esa forma lagunas en la continuación del tratamiento que debe recibir todo paciente, y a la misma vez distorcionando la relación que debe existir entre médico y paciente.

Las ideas que antes apuntamos las hicimos llegar también en una entrevista personal con el Sr. Concepción Pérez Pérez, Administrador del Fondo del Seguro del Estado, al Secretario del Trabajo y a los gerentes de seguros de vida. También sometimos al señor Pérez un memorando relacionando estas ideas, a las que prometió darle cuidadoso estudio.

VI. *Asociación de Alcaldes:*

Durante el pasado año hemos tenido la oportunidad de reunirnos en varias ocasiones con miembros de la directiva de la Asociación de Alcaldes de Puerto Rico. En estas ocasiones hemos discutido los problemas con que nuestros amigos alcaldes se enfrentan al tratar de descargar sus responsabilidades con relación a la salud de sus poblaciones respectivas. Es interesante señalar que mientras el alcalde se enfrenta directamente a los problemas de salud que continuamente son traídos a su atención, la autoridad y el poder

económico para solucionar esos problemas han sido quitados de sus manos y residen en un funcionario de la oficina central en el Departamento de Salud, que radica en San Juan, lejos de donde el problema ha surgido.

También discutimos con los miembros de la Asociación de Alcaldes el problema que presentan aquellos compañeros médicos que por falta de orientación adecuada regresan a Puerto Rico debidamente titulados pero que no pueden tomar sus exámenes de reválida por no haber completado los requisitos de ley. En estas conversaciones han participado también representantes del Departamento de Salud, del Tribunal Examinador de Médicos y de la Escuela de Medicina. Esperamos que estas conversaciones provean la oportunidad para solucionar el problema con que se enfrentan estos compañeros. Cursos se están elaborando por esfuerzos comunes a ese fin. La Escuela de Medicina de la Universidad de Puerto Rico se está distinguiendo en esta encuesta.

VII. *ECFMG en español:*

En nuestro esfuerzo por implementar la resolución que a este efecto aprobara la Cámara de Delegados en noviembre de 1965, hemos continuado nuestras conversaciones tendientes a lograr que el examen ofrecido por el "Educational Council for Foreign Medical Graduates" sea ofrecido a los estudiantes de habla española. Ya conversamos con representantes de dicho Concilio y de la Asociación Médica Americana. En la próxima reunión de la Junta de Directores del ECFMG tendremos la oportunidad de comparecer para presentar ante ellos nuestra petición. También hemos sometido un memorando al respecto al Dr. F. J. L. Blassingame, Vicepresidente Ejecutivo de la AMA, quien prometió brindar toda su cooperación para lograr este propósito y quizás sea la AMA quien nos dé voz en estas deliberaciones.

VIII. *Conversión de hospitales privados a hospitales de la comunidad:*

Entendiendo que lo hacemos en beneficio tanto de la clase médica en general como de algunos compañeros en particular, hemos estado en conversaciones con algunos dueños de hospitales estudiando la idea de que conviertan sus instituciones en hospitales de la comunidad. Aunque por el momento no hemos logrado acción definitiva sobre el asunto, sí hemos despertado en estos compañeros la inquietud intelectual para pensar en la conveniencia de esta idea. Deseo hacer énfasis ante ustedes que no debemos olvidar esta oportunidad que tenemos de ayudar a despertar en nuestra comunidad la consciencia de que los ciudadanos particulares, tanto o más que el gobierno propio, son responsables de la salud del pueblo. Es preciso que nos despojemos de esa sumisa aceptación a la política paternalista de nuestro gobierno en el campo de la salud y que como médicos y a la vez ciudadanos asumamos nuestra responsabilidad de asumir liderato con referencia a los problemas de salud.

IX. *Seminario sobre hospitales:*

El pasado jueves 27 de octubre de 1966 se celebró en nuestros salones un seminario sobre hospitales, auspiciado por la Asociación de Hospitales, la Asociación de Administradores de Hospitales, el Concilio de Salud y la Asociación Médica de Puerto Rico. A esta actividad invitamos los miembros de la junta de directores de hospitales, directores médicos, administradores, presidentes de facultades médicas y otros miembros de la comunidad interesados en el campo de hospitales. A través de dos paneles celebrados se tuvo la oportunidad de discutir varios puntos de interés común para los presentes. Con gran satisfacción podemos informar que esta acti-

vidad redundó en un sólido éxito para la Asociación Médica de Puerto Rico y que fueron muchas las personas que se acercaron a nosotros para manifestarnos el provecho que habían recibido de estas discusiones. Entre los panelistas se encontraron personalidades de diferentes campos de nuestra vida pública. El sólo hecho de reunir a una concurrencia de tan variados intereses bajo nuestro techo para pensar en los problemas de la salud de nuestro pueblo, constituye de por sí un gran triunfo para la Asociación Médica de Puerto Rico. La idea de que médicos formen parte de las juntas de directores de los hospitales se impulsó en esta reunión.

X. *Hospitales de la comunidad en el Centro Médico:*

Justamente el pasado jueves, 10 de noviembre, nos reunimos en la Asociación Médica de Puerto Rico con varios compañeros para discutir la posibilidad de que se establezca en el Centro Médico de Puerto Rico un hospital de la comunidad que permita tanto a los médicos que participan en actividades académicas en la Escuela de Medicina así como aquellos miembros de otras facultades médicas de instituciones pertenecientes al Centro Médico y a médicos de la comunidad en general, hospitalizar pacientes solventes en esta institución. Entre los presentes estuvieron el Dr. José R. Vivas, el Dr. Adán Nigaglioni, el Sr. Julio A. Pérez, varios profesores y jefes de departamentos de la Escuela de Medicina, y otros compañeros interesados. De estas conversaciones deberá surgir una institución que sirva adecuadamente los intereses de la comunidad de aquel sector. Es preciso que la Asociación Médica de Puerto Rico se esfuerce porque los estudiantes que pasan por nuestra Escuela de Medicina estén en contacto durante su vida estudiantil y años de formación médica no solamente con el sector gubernamental de nuestras instituciones hospitalarias sino que también observen y participen en la manera cómo la medicina privada se ejerce en nuestra Isla.

XI. *Otras actividades:*

1. Durante el pasado año tuvimos la oportunidad de tener la visita a Puerto Rico del Dr. F. J. L. Blassingame, Vicepresidente Ejecutivo de la "American Medical Association". El doctor Blassingame se reunió con los miembros de la Junta de Directores y otros compañeros, teniendo la oportunidad de conocer más de cerca los problemas con que nos enfrentamos en Puerto Rico.

2. En el mes de septiembre del 1966 se reunió en San Juan durante un fin de semana la Junta de Directores de la Asociación Médica del estado de Florida. Pudimos compartir con estos compañeros tanto en reuniones de negocios como en actos sociales, estrechando así los lazos de confraternidad con estos compañeros médicos. Fue interesante el comentario hecho por uno de los amigos de Florida después de escuchar nuestra exposición sobre los problemas con que nos enfrentamos los médicos puertorriqueños. Indicó el amigo de Florida que mientras en los Estados Unidos se luchaba por evitar caer en la medicina socializada, en Puerto Rico la Asociación Médica local se esforzaba por librar a nuestro pueblo de la medicina socializada.

3. La Asociación de Enfermeras Graduadas de Puerto Rico celebró recientemente su Jubileo de Oro. En esa ocasión hicimos llegar a nuestras eficientes colaboradoras el testimonio de aprecio de la clase Médica de Puerto Rico.

4. Recientemente se inauguró el dispen-

sario Dr. Manuel Díaz García, que radica frente a nuestro edificio. Estuvieron presentes en esa ocasión el Sr. Gobernador de Puerto Rico, la Alcaldesa de la Capital y otros distinguidos dignatarios de nuestro Gobierno. Al participar en este programa manifestamos a los allí presentes el deseo de la Asociación Médica de Puerto Rico de que muy pronto se haga innecesaria la construcción de este tipo de facilidades como consecuencia de que nuestra población adquiera la habilidad para escoger libremente su propio médico.

5. Recientemente visitó a Puerto Rico el grupo conocido como Sing Out — 66. Primeramente tuvimos la oportunidad de ver este grupo cuando se presentaron durante la Sesión Inaugural de la Convención Anual de la Asociación Médica Americana celebrada en Chicago, en junio de 1966. Al surgir la idea de que este grupo viniera a Puerto Rico, la Asociación Médica de Puerto Rico participó a través de diferentes compañeros en las gestiones necesarias para que nuestra juventud tuviera la oportunidad de conocer un grupo de tan altos principios como éste.

XII. *Recopilación de resoluciones:*

Deseamos aquí hacer público reconocimiento de la labor realizada por el compañero Walter J. Benavent, Presidente del Consejo Judicial y Administrativo, al recopilar y catalogar por tópico los acuerdos tomados por la Cámara de Delegados de la Asociación Médica de Puerto Rico en los años más recientes. El compañero Benavent no se encuentra hoy entre nosotros por motivos de salud, según indicáramos anteriormente. Sin embargo, queremos hacer mención específica de la excelente labor rendida por él al hacer esta recopilación.

XIII. *Abortos:*

Entregamos al Hon. Secretario de Salud las enmiendas que la AMPR le ofrece para incorporar al Reglamento de Hospitales. Estas enmiendas fortalecen la posición del Departamento de Salud en cuanto al problema de los abortos. Copia de estas enmiendas propuestas se le enviaron al Hon. Secretario de Justicia según nuestro compromiso.

XIV. *Estadísticas:*

¡Cuánta falta nos hacen! Los números convencen. Eso de que el 69% de los ciudadanos de 65 años o más de los que votaron por la medicina nuestra, a 183 el voto por mes... Eso de que sólo una Asociación Médica Estatal votó a favor del Título XVIII-B... Esto de que más del 50% de la población de Puerto Rico es medianamente solvente:

10% de la población de Puerto Rico	250,000
Cruz Azul	145,000
Triple S	110,000
Cooperativa de Salud	60,000
Asociación de Maestros	38,000
Plan Servicio Médico Hospitalario	80,000
Medicare	150,000
Planes Privados Prepagos Más de	100,000
Auxilio Mutuo	8,000
Veteranos	130,000
Fondo del Seguro del Estado — si se amplía	250,000
Uniones, más de	100,000

y si a estos números le puediéramos sumar los beneficiados por el Título XIX (500,000).

Mil veces hemos recitado estas estadísticas. Mil veces más las repetiremos. Son verdades.

Tercera Parte

Recomendaciones Futuras:

Transcurrida la experiencia de un año en la presidencia de la Asociación Médica de Puerto Rico, nuestra conciencia despierta

a varios asuntos que por su vital importancia deben quedar claramente ante la atención de la clase médica de Puerto Rico. Entre ellos podemos señalar los siguientes:

1. Administración y facilidades de la Asociación Médica de Puerto Rico: Tenemos que comprender y enfrentarnos al hecho de que la realización de los diferentes programas en que nos hemos empeñado conlleva la necesidad de una estructura administrativa y facilidades físicas necesarias para poder llevarlas a cabo. Es necesario reevaluar los instrumentos que proveemos a nuestros presidentes, a miembros de la directiva central, a comités y secciones. Será necesaria una inversión sustancial para dotar a la Asociación Médica de Puerto Rico de facilidades de oficina y personal profesional adecuados. Cuando hablo de personal profesional me refiero al conjunto ejecutivo, no necesariamente médico, profesional, que en la escala de nuestra organización esté colocado intermedio entre el conjunto secretarial y el conjunto directivo médico de la Asociación. Esto cuesta dinero. Pero nuestra eficiencia y efectividad en el desarrollo de programas depende de ello. Recomiendo que se nombre un comité por esta Cámara de Delegados para que dé atención específica y particular a este problema.

2. Implementación del Título XIX de la Ley Medicare en Puerto Rico: Según ya apuntáramos, éste es el problema principal con que actualmente se confronta la Asociación Médica de Puerto Rico. No podemos descuidar nuestra atención a las implicaciones que una implementación equivocada de este programa podrían tener para el pueblo pobre de Puerto Rico. Es por eso que debemos continuar nuestras gestiones ante las autoridades federales y locales, insistiendo en que se le dé vida al espíritu con que esta legislación fue aprobada. Es posible que esta Cámara considere necesario la creación de un comité dentro del seno de esta Asociación que se dedique única y exclusivamente a seguir de cerca los nuevos desarrollos que en torno a este programa vayan surgiendo. A su vez este comité quizás vea la necesidad de consultar expertos en la materia, contratar servicios para conseguir estudios, estadísticas, etc. El concepto del Dr. Egidio Colón Rivera de continuidad y especialización, es importantísimo. Deberemos pedir vistas o reuniones con el Comité Asesor del Título XIX, el cual fue nombrado en agosto del 1966, cuando debió haber sido nombrado antes de hacerse el plan, y que aún no se ha reunido.

3. La conversión de hospitales privados con fines de lucro a hospitales de la comunidad conllevaría la posibilidad de convertir hospitales gubernamentales a hospitales de la comunidad. Deberemos reunirnos con el Comité Asesor del Programa de Construcción de Hospitales.

4. Etc. (No duplicaré lo ya comentado y lo informado por otros colegas de otros consejos y comités).

5. Participación en problemas socio-económicos de Puerto Rico: Es interesante observar cómo la Asociación Médica Americana, que surgiera originalmente como una entidad puramente científica, ha ido evolucionando hacia convertirse en la voz de la clase médica americana, que se hace oir cuando se baten los problemas socio-económicos de la nación. En igual forma la Asociación Médica de Puerto Rico, sin olvidar su vida científica y profesional, debe continuar participando y expresándose cada vez más con relación a los problemas con que se enfrenta nuestra sociedad hoy en día y que afectan la vida económica y social del país. No podemos vivir dentro de la concha resguarda-

dora de nuestra profesión. Tenemos que participar e influenciar en todo lo posible las actividades del resto de nuestra sociedad, particularmente en cuanto a asuntos de salud. Todos habrán de escuchar y comprender la filosofía de la clase médica.

Nuestro es el partido de la salud. El pueblo nos ha dado su voto. El mandato es nuestro.

Con este informe toca a su fin el año durante el cual ustedes me confiaron la presidencia de la Asociación Médica de Puerto Rico. Al pasar balance nos impresiona más lo mucho que aparece bajo la columna "Debe" que lo poco bajo la columna "Haber". Ruego la benevolencia de todos por los errores cometidos; espero todos aprendamos de ellos. El poder haberles servido en esta presidencia ha sido el honor más grande de mi vida. Muchas Gracias.

EDITORIAL

NUESTRAS METAS

> Nosotros vamos tejiendo nuestra historia y somos creadores de nuestra suerte y futuro.

Nuestra profesión está atravesando al presente por un período de transición de vital importancia para la salud de nuestros pacientes. Originalmente la preocupación principal del médico era la terapéutica, debido a que desconocía las causas de las enfermedades el médico trataba a su paciente sintomáticamente. Luego pasamos a la época donde el médico a través del descubrimiento de bacterias le dio importancia a la etiología de las enfermedades. Más tarde se le dio énfasis a la medicina preventiva y la salud pública. Pasamos de ahí a la era de la medicina psicosomática. Hemos entrado recientemente a la quinta etapa de esta metamorfosis gradual en la cual los médicos tenemos que dedicarle más y más tiempo a nuestra responsabilidad social en los problemas públicos. Hoy día el médico como ciudadano responsable tiene que lanzarse a dialogar y batallar en pro de la práctica libre y democrática de la medicina, la cual es de vital importancia para la buena salud de nuestros pacientes.

Hemos visto en los últimos años la marcada tendencia de nuestros gobiernos en resolver, a su manera, los problemas de salud de nuestros pacientes. Se ha hablado demasiado sobre los efectos que han causado nuestros gobiernos sobre nuestros pacientes y sobre nuestra profesión. Ha llegado el momento de dejarnos de lamentar, de quejarnos, de que nos den úlceras, trombosis, canas y de estar mirando al pasado.

Compañeros, ha llegado el momento de acción social positiva *dentro de un marco cristiano y democrático. Nuestro potencial individual y de grupo es infinito. Además de atender con diligencia a nuestros pacientes y sus familiares tenemos que recetarlos cívicamente sobre los graves problemas actuales de salud de nuestra Isla.*

Le reto a lograr las siguientes metas:

1. Predicar a diario nuestra posición: Queremos que cada puertorriqueño reciba la mejor calidad de servicios médicos independientemente de su condición social, económica, de su raza, de sus creencias religiosas y políticas.

2. Fomentar entre nuestros compatriotas el ciudadano independiente, alerta, responsable de sus obligaciones para con Dios, familia, él y su país, ayudando por todos los medios a nuestro alcance al ciudadano que quiere y desee ayudarse.

3. Incrementar nuestros esfuerzos para identificarnos con los problemas de salud de nuestro pueblo, asumiendo el liderato y a la ofensiva en la búsqueda de soluciones puertorriqueñas a nuestros problemas.

4. Presentarle a nuestro pueblo programas de salud constructivos, factibles, positivos y a tono con nuestras actuales y futuras necesidades.

5. Llamar a los médicos de Puerto Rico a lo que denominaremos "Operación Unidad".

6. Recalcar una y otra vez las ventajas obvias del sistema de libre selección de médico y hospital.

7. Propulsar a todo vapor el seguro médico voluntario *prepagado con miras a lograr pronto lo que denominaremos "Operación Igualdad".*

8. Fomentar la construcción de hospitales de la comunidad de tan vital importancia para la salud de nuestro pueblo.

9. Participar activamente en las diferentes agrupaciones cívicas y en el partido político de su preferencia fomentando la "Operación Cultivación".

10. Honrar los Mandamientos de la ley de Dios y los principios de ética médica.

Estoy positivamente seguro de que si logramos estas metas estaremos preservando y fomentando la buena salud de nuestro pueblo, la cual es oro de buena ley. Nos encontramos en una posición envidiable para influenciar a nuestros compatriotas, ya que nosotros jugamos un rol dual de ciudadano y de médico. Todo depende de nosotros.

Les exhorto de todo corazón a que luchemos hombro con hombro, unidos en pro de la causa de nuestros pacientes, la cual redundará en beneficios positivos en pro de la salud y el bienestar de todo el pueblo de Puerto Rico.

Luis A. Izquierdo Mora, M. D.
Presidente
Asociación Médica de Puerto Rico

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